U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
MATSUOKA=18

U S APPLICATION NO (If known,see 37 CFR 1 5)
09/890219

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY CLAIMED
PCT/JP00/00444	28 January ~~1999~~ 2000	28 January 1999

TITLE OF INVENTION
SUBSTITUTED PHENETHYLAMINE DERIVATIVES

APPLICANT(S) FOR DO/EO/US
Hiroharu MATSUOKA et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] The US has been elected in a Demand by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a [ ] is attached hereto (required only if not transmitted by the International Bureau).
   b [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An Assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment
    [X] A SECOND or SUBSEQUENT preliminary amendment
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    [X] Courtesy copy of the first page of the International Publication (WO 00/44770).
    [X] Courtesy copy of the Translation of the International Preliminary Examination Report. There were no annexes
    [X] Courtesy Copy of the International Search Report.
    [X] Application Data Sheet.
    [X] The application is (or will be) assigned to: CHUGAI SEIYAKU KABUSHIKI KAISHA, whose address is 5-1, Ukima 5-chome, Kita-ku, Tokyo 115-8543, Japan.

JC17 Rec'd PCT/PTO 27 JUL 2001

U.S. APPLICATION NO (If known, see 37 CFR 1 5)	International Application No	Attorney's Docket No
09/890219	PCT/JP00/00444	MATSUOKA=18

17. [xx] The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a)(1) –(5):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO................**$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO...........**$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO...................**$710.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)................**$690.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).........................**$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [X] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
Claims as Originally Presented	Number Filed	Number Extra	Rate		
Total Claims	32 - 20	12	X $18.00	$ 216.00	
Independent Claims	1 - 3		X $80.00	$	
Multiple Dependent Claims (if applicable)			+$270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1,206.00	
Claims After Post Filing Prel. Amend	Number Filed	Number Extra	Rate		
Total Claims	34 - 32	2	X $18.00	$ 36.00	
Independent Claims	1 - 3		X $78.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1,242.00	
Reduction of ½ for filing by small entity, if applicable. Applicant claims small entity status. See 37 CFR 1.27.				$	
SUBTOTAL =				$1,242.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$1,242.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$1,242.00	
				Amount to be: refunded	$
				charged	$

a. [ ] A check in the amount of $____________ to cover the above fees is enclosed.
b. [X] Credit Card Payment Form (PTO-2038), authorizing payment in the amount of $ 1,242.00, is attached.
c. [ ] Please charge my Deposit Account No. **02-4035** in the amount of $____________ to cover the above fees. A duplicate copy of this sheet is enclosed.
d. **[XX]** The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **02-4035** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, N.W., SUITE 300
WASHINGTON, D.C. 20001
TEL: (202) 628-5197
FAX: (202) 737-3528

Date of this submission: **July 27, 2001**

Roger L. Browdy
SIGNATURE

Roger L. Browdy
NAME

25,618
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.=S DOCKET: MATSUOKA18

In re Application of:	Art Unit:
Hiroharu MATSUOKA, et al.	Examiner:
Serial No.: not yet received	Confirmation No.
Filed: even date herewith	Washington D.C.
For: SUBSTITUTED PHENETHYLAMINE DERIVATIVES	July 26, 2001

SUPPLEMENTAL PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination upon the merits, kindly amend as follows:

IN THE SPECIFICATION

After the title please insert the follwing paragraph:
REFERENCE TO RELATED APPLICATIONS

--The present application is the national stage under 35 U.S.C. §371 of international application PCT/JP00/00444, filed January 28, 2000 which designated the United States, and which application was not published in the English language.--

Page 42, please amend Table A-8 as follows:

Table A-8

Example No.	Structural formula or chemical name
126	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$
127	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$
128	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$
129	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$
130	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$
131	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$
132	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$
133	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide
134	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide
135	ethyl 2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl] propanoyl)piperazinyl]acetate
136	2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetic acid
137	Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH_2
138	Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH_2
139	Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH_2
140	Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH_2

Page 43, please amend Table A-9 as follows:

Table A-9

Example No.	Structural formula or chemical name
141	Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH_2
142	Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH_2
143	Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH_2
144	Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH_2
145	Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH_2
146	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide
147	(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide
148	Phe(4-F)-N-Me-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2
149	Phe(4-F)-N-Me-D-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2
150	Phe(4-F)-N-Me-Ala(□-CF_3)-N-Me-Tyr(3-tBu)-NH_2
151	Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH_2
152	Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH_2
153	Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH_2
154	Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH_2
155	Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH_2
156	Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH_2
157	Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
158	Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
159	Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
160	Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
161	Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH_2
162	Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH_2
163	Phe(4-F)-N-Me-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2

Page 106, please amend paragraph 1 as follows:

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

Page 257, please amend Table E-7 as follows:

Table E-7

Intermediate T14

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-[4-(methylsulfonyl)piperazinyl]propane-1-one

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Boc-piperazine (g)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	0.700	0.36	0.42	15.00	20	nHx:EA=1:1	I-a(7)	1.900

Reaction 2

Compound I-a(7) (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.900	5.00	20.00	4	MC:MeOH=20:1	I-b(7)	1.400

Reaction 3

Compound I-b(7) (g)	$ClSO_2Me$ (ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	0.46	0.82	20.00	2	MC:MeOH =20:1	I-c(7)	1.500

Reaction 4

Compound I-c(7) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	0.300	20.00	20	MC:MeOH =20:1	0.900

IN THE CLAIMS

Please add the following claims:

35. (New) A method for treating a patient suffering from hypermotilinemia comprising administering to said patient an effective amount of a compound according to claim 1.

36. (New) A method for suppressing gastrointestinal motility in a patient suffering therefrom comprising administering to said patient an effective amount of a compound according to claim 1.

REMARKS

Claims 1-25 and 28-36 presently appear in this case. The above amendments to the specification are being made in order to correct several self-evident typographical errors. The amendments to the claims are being made in order to add new claims.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**."

Favorable consideration is earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: [signature]
Roger L. Browdy
Registration No. 25,618

RLB:wrd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
F:\,Y\YUAS\mATSUOKA 18\Pto\Sup. Pre. Amendment.doc

Version with markings to show changes

IN THE SPECIFICATION

A paragraph was added after the title.

Page 42, please amend Table A-8 as follows:

Table A-8

Example No.	Structural formula or chemical name
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133	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide
134	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide
135	ethyl 2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl] **propanoyl** ~~propanoly~~)piperazinyl]acetate
136	2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl]**propanoyl** ~~propanoly~~)piperazinyl]acetic acid
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147	(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-**methylpropanoylamino** ~~methylpropanolyamino~~]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide
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152	Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH_2
153	Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH_2
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157	Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
158	Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
159	Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
160	Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
161	Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH_2
162	Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH_2
163	Phe(4-F)-N-Me-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2

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To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

Page 257, please amend Table E-7 as follows:

Table E-7

Intermediate T14

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-[4-(methylsulfonyl)piperazinyl ~~piperazineyl~~]propane-1-one

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Boc-piperazine (g)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	0.700	0.36	0.42	15.00	20	nHx:EA=1:1	I-a(7)	1.900

Reaction 2

Compound I-a(7) (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.900	5.00	20.00	4	MC:MeOH=20:1	I-b(7)	1.400

Reaction 3

Compound I-b(7) (g)	$ClSO_2Me$ (ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	0.46	0.82	20.00	2	MC:MeOH =20:1	I-c(7)	1.500

Reaction 4

Compound I-c(7) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	0.300	20.00	20	MC:MeOH =20:1	0.900

IN THE CLAIMS

New claims 35 and 36 were added.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.=S DOCKET: MATSUOKA18

In re Application of:	Art Unit:
Hiroharu MATSUOKA, et al.	Examiner:
Serial No.: not yet received	Confirmation No.
Filed: even date herewith	Washington D.C.
For: SUBSTITUTED PHENETHYLAMINE DERIVATIVES	July 26, 2001

PRELIMINARY AMENDMENT

Honorable Commissioner for Patents
Washington, D.C. 20231

Contemporaneous with the filing of this case and prior to calculation of the filing fee, kindly amend as follows:

IN THE CLAIMS

Please amend claim 13 as follows:

13. (Amended) The compound according to claim 1, wherein R_6 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 14 as follows:

14. (Amended) The compound according to claim 1, wherein R_7 in Formula (1) is hydrogen or optionally substituted amino;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 15 as follows:

15. (Amended) The compound according to claim 1, wherein R_8 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 16 as follows:

16. (Amended) The compound according to claim 1, wherein R_9 in Formula (1) is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, cyclohexylmethyl or para-fluorobenzyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 17 as follows:

17. (Amended) The compound according to claim 1, wherein R_{20} in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 18 as follows:

18. (Amended) The compound according to claim 1, wherein R_{10} in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 19 as follows:

19. (Amended) The compound according to claim 1, wherein R_{11} in Formula (1) is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl,

ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tertbutylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl, 6-methyl-4-pyrimidinon-2-yl, methylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl or 4-methylsulfonyl-1-piperazinecarbonyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 20 as follows:

20. (Amended) The compound according to claim 1, wherein R_{12} in Formula (1) is hydroxy;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 21 as follows:

21.(Amended) The compound according to claim 1, wherein R_{13} in Formula (1) is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;
or a hydrate or pharmaceutically acceptable salt thereof.

Please amend claim 24 as follows:

24. (Amended) A medicine containing an effective amount of the compound according to claim 1 as an active ingredient.

Please amend claim 25 as follows:

25. (Amended) A motilin receptor antagonist composition containing an effective amount of the compound according to claim 1.

Cancel claims 26 and 27 without prejudice or disclaimer.

REMARKS

Claims 1-25 and 28-34 presently appear in this case. The above amendments to the claims are being made in order to eliminate any properly multiply dependent claims, for the purpose of reducing the filing fee. Please enter this amendment prior to calculation of the filing fee in this case.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**."

Respectfully submitted,

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Version with markings to show changes@

IN THE CLAIMS

13. The compound according to ~~any one of claims 1-12~~ claim 1, wherein R_6 in Formula (1) is hydrogen or methyl; or a hydrate or pharmaceutically acceptable salt thereof.

14. The compound according to ~~any one of claims 1-13~~claim 1, wherein R_7 in Formula (1) is hydrogen or optionally substituted amino;
or a hydrate or pharmaceutically acceptable salt thereof.

15. The compound according to ~~any one of claims 1-14~~claim 1, wherein R_8 in Formula (1) is hydrogen or methyl; or a hydrate or pharmaceutically acceptable salt thereof.

16. The compound according to claim 1~~any one of claims 1-15~~, wherein R_9 in Formula (1) is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, cyclohexylmethyl or para-fluorobenzyl;
or a hydrate or pharmaceutically acceptable salt thereof.

17. The compound according to ~~any one of claims 1-16~~claim 1, wherein R_{20} in Formula (1) is hydrogen or methyl; or a hydrate or pharmaceutically acceptable salt thereof.

18. The compound according to ~~any one of claims 1-17~~claim 1, wherein R_{10} in Formula (1) is hydrogen or methyl; or a hydrate or pharmaceutically acceptable salt thereof.

19. The compound according to ~~any one of claims 1-18~~claim 1, wherein R_{11} in Formula (1) is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tertbutylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl, 6-methyl-4-pyrimidinon-2-yl, methylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl or 4-methylsulfonyl-1-piperazinecarbonyl; or a hydrate or pharmaceutically acceptable salt thereof.

20. The compound according to ~~any one of claims 1-19~~claim 1, wherein R_{12} in Formula (1) is hydroxy; or a hydrate or pharmaceutically acceptable salt thereof.

21. The compound according to ~~any one of claims 1-20~~claim 1, wherein R_{13} in Formula (1) is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl; or a hydrate or pharmaceutically acceptable salt thereof.

24. A medicine containing **an effective amount of** the compound according to ~~any one of claims 1-23~~claim 1 as an active ingredient.

25. A motilin receptor antagonist **composition** containing **an effective amount of** the compound according to ~~any one of claims 1-23~~claim 1.

09/890219
JC17 Rec'd PCT/PTO 27 JUL 2001

SPECIFICATION

SUBSTITUTED PHENETHYLAMINE DERIVATIVES

TECHNICAL FIELD

This invention relates to substituted phenethylamine derivatives that function as a motilin receptor antagonist and that are useful as medicines.

BACKGROUND ART

Motilin, which is one of the gastrointestinal hormones, is a straight-chained peptide consisting of 22 amino acids and is well known to be responsible for regulating the motility of the gastrointestinal tract in animals including human. It has been reported that exogenously administered motilin causes contractions in humans and dogs that are similar to interdigestive migrating contractions, thus promoting gastric emptying (Itoh et al., Scand. J. Gastroenterol., 11, 93-110 (1976); Peeters et al., Gastroenterology 102, 97-101 (1992)). Hence, erythromycin derivatives which are an agonist of motilin are under development as an gastrointestinal tract motor activity enhancer (Satoh et al., J. Pharmacol. Exp. Therap., 271, 574-579 (1994); Lartey et al., J. Med. Chem., 38, 1793-1798 (1995); Drug of the Future, 19, 910-912 (1994)).

Peptide and polypeptide derivatives have been reported as antagonists of motilin receptors (Depoortere et

al., Eur. J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem. Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al., J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These derivatives are used as a pharmacological tool in the study of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

Motilin receptors had been known to occur principally in the duodenum but recently it has been shown that they also occur in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that motilin is involved not only in the motility of the upper part of the gastrointestinal tract but also in the motility of its lower part.

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome who were manifesting diarrhea and in patients with irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease. Other diseases that have been reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy

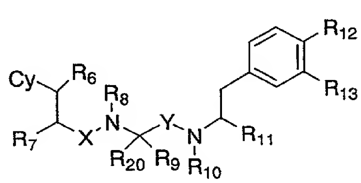
syndrome. The antagonists of motilin receptors have the potential to ameliorate irritable bowel syndrome and other diseased states accompanied by increased blood motilin levels.

DISCLOSURE OF INVENTION

An object of the present invention is to provide substituted phenethylamine derivatives that function as an antagonist of motilin receptors and which are useful as medicines.

The present inventors conducted repeated intensive studies in an attempt to develop compounds having an outstanding motilin receptor antagonistic action. As a result, they found that substituted phenethylamine derivatives represented by Formula (1) were an excellent antagonist of motilin receptors. The present invention has been accomplished on the basis of this finding.

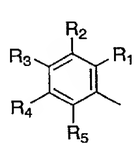
Thus, the present invention provides compounds of Formula (1):



(1)

wherein:

Cy is a group of Formula (2):



(2)

an optionally substituted heterocyclic ring, C_{3-7}cycloalkyl or phenyl;

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy, amino, trifluoromethyl or nitrile and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen, trifluoromethyl or nitrile;

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

R_7 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

R_8 is hydrogen, methyl or ethyl;

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, optionally substituted straight-chained or branched C_{2-6}alkenyl, optionally substituted straight-chained or branched C_{2-6}alkynyl, C_{3-7}cycloalkyl or optionally substituted phenyl;

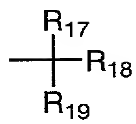
R_{20} is hydrogen or straight-chained or branched C_{1-3}alkyl or R_9 and R_{20} may together form C_{3-7}cycloalkyl;

R_{10} is hydrogen or straight-chained or branched C_{1-3}alkyl;

R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, $-CO-N(R_{14})R_{15}$, carboxyl or an optionally substituted heterocyclic ring;

R_{12} is hydroxy or $-OR_{16}$;

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl, straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (3):



(3)

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4}alkyl, C_{3-7}cycloalkyl, straight-chained or branched C_{1-4}alkyloxy, straight-chained or branched C_{1-4}alkylsulfonyl or a heterocyclic ring, or R_{14} and R_{15}, as -$N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

R_{16} is straight-chained C_{1-4}alkyl;

R_{17} is hydrogen or methyl;

R_{18} and R_{19} together form cycloalkyl or C_{3-7}cycloalkenyl;

X is carbonyl or methylene;

Y is carbonyl or methylene;

provided that

when Cy is 3-indolyl,

(i) R_{11} is an optionally substituted heterocyclic ring; or

(ii) R_6 is hydrogen, R_7 is amino, R_8 is methyl, R_9 is isopropyl, R_{20} is hydrogen, R_{10} is methyl, R_{11} is carbamoyl, R_{12} is hydroxy, R_{13} is tert-butyl, X is carbonyl and Y is carbonyl, and

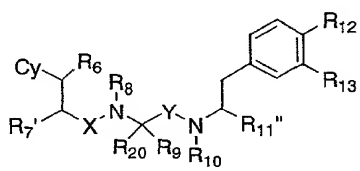
when Cy is cyclohexyl or phenyl, R_{11} is an optionally substituted heterocyclic ring,

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides a medicine

containing a compound of Formula (1) as an active ingredient. Further, the present invention provides a motilin receptor antagonist composition containing the compound. The present invention also provides a gastrointestinal motility suppressor agent containing the compound as an active ingredient. Further, the present invention provides a therapeutic of hypermotilinemia containing the compound as an active ingredient.

The present invention also provides compounds of Formula (4):



(4)

wherein

Cy, R_6, R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13}, X and Y are as defined in claim 1;

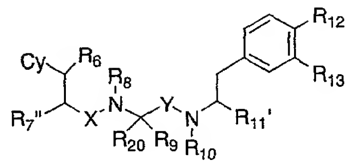
R_7' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one protected substituent, amino optionally having at least one protected substituent or protected hydroxy;

R_{11}" is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15}, wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having protected amino or an optionally substituted heterocyclic ring;

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of

Formula (5):



(5)

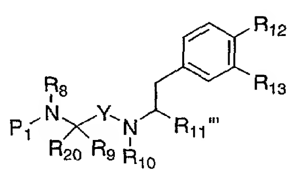
wherein:

Cy, R_6, R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13}, X and Y are as defined in claim 1;

R_7" is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy;

R_{11}' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one protected substituent, $-CO-N(R_{14})R_{15}$ wherein R_{14} and R_{15} are as defined in claim 1, carboxyl or an optionally substituted heterocyclic ring; or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (6):



(6)

wherein:

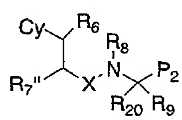
R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13} and Y are as defined in claim 1;

P_1 is hydrogen or a protecting group of amine;

R_{11}''' is hydrogen, optionally substituted straight-

chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15} wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having protected amino or an optionally substituted heterocyclic ring;
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (7):



(7)

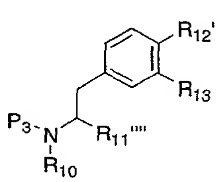
wherein:

Cy, R_6, R_8, R_9, R_{20} and X are as defined in claim 1;

R_7" is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy;

P_2 is optionally protected carboxyl, formyl or methyl having a leaving group;
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (8)



(8)

wherein:

R_{10} and R_{13} are as defined in claim 1;

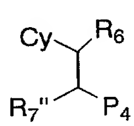
P_3 is hydrogen or a protecting group of amine;

R_{11}'''' is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, $-CO-N(R_{14})R_{15}$ wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having protected amino or an optionally substituted heterocyclic ring;

R_{12}' is hydroxy or $-OR_{16}$ wherein R_{16} is as defined in claim 1;

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (9)



(9)

wherein:

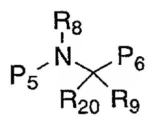
Cy and R_6 are as defined in claim 1;

R_7'' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy;

P_4 is optionally protected carboxyl, formyl or methyl having a leaving group;

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (10)



(10)

wherein:

R_8, R_9 and R_{20} are as defined in claim 1;

P_5 is hydrogen or a protecting group of amine;

P_6 is optionally protected carboxyl, formyl or methyl having a leaving group;

or hydrates or pharmaceutically acceptable salts thereof.

In the definition of the compounds of Formula (1), halogen as R_1, R_2, R_3, R_4 and R_5 of Formula (2) as Cy is preferably fluorine or chlorine, with fluorine being more preferred. When at least 2 of R_1 to R_5 are halogen, they may be the same or different halogen, however it is preferable that they are the same. The number of halogen atoms is preferably 1 to 3 and more preferably 1 or 2.

Preferably, at least one of R_1, R_2, R_3, R_4 and R_5 of Formula (2) as Cy is halogen, trifluoromethyl or nitrile and the others are independently hydrogen or hydroxy. Preferably, R_3 is halogen, trifluoromethyl or nitrile or R_2 and R_3 are the same kind of halogen. Preferred compounds include those in which R_3 is halogen and R_1, R_2, R_4 and R_5 are hydrogen; those in which R_2 and R_3 are the same halogen and R_1, R_4 and R_5 are hydrogen; and those in which at least one of R_1, R_2, R_3, R_4 and R_5 is trifluoromethyl or nitrile and the others are hydrogen, halogen or hydroxy.

Preferred examples of the group of Formula (2) as Cy include 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl and 4-cyanophenyl, more preferably 4-fluorophenyl and 4-chlorophenyl, with 4-fluorophenyl being most preferred.

Preferred examples of the heterocyclic ring of the optionally substituted heterocyclic ring as Cy include aliphatic or aromatic 5- to 7-membered mono- or fused-rings containing at least one hetero atom selected from among N, S and O; specific examples include pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, indolyl, quinolinyl, benzoimidazolyl, benzodiazepinyl, benzofuryl, pyrrolidinyl, piperazinyl, piperidinyl and tetrahydroisoquinolinyl, with indolyl being preferred.

Exemplary substituents of the optionally substituted heterocyclic ring as Cy include hydroxy, methoxy, amino, methyl, ethyl, trifluoromethyl, carboxy, methoxycarbonyl and oxo. The heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different.

Preferably, the optionally substituted heterocyclic ring of Cy is 3-indolyl.

Preferably, the C_{3-7}cycloalkyl as Cy is cyclopentyl or cyclohexyl.

While Cy has the definitions set forth above, Cy is preferably Formula (2) or an optionally substituted

heterocyclic ring, more preferably 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl and 3-indolyl, with 4-fluorophenyl being particularly preferred.

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl or ethyl.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl, ethyl, fluoromethyl or trifluoromethyl, with methyl being particularly preferred.

While R_6 has the definitions set forth above, R_6 is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 is preferably methyl.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 include halogen, hydroxy and amino, with hydroxy being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or

branched C_{1-3}alkyl as R_7 is preferably methyl or trifluoromethyl, with methyl being particularly preferred.

Exemplary substituents of the optionally substituted amino as R_7 include straight-chained or branched C_{1-3}alkyl, with methyl and ethyl being preferred. The amino may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted amino as R_7 is preferably amino optionally substituted with one or more of the same or different kinds of straight-chained or branched C_{1-3}alkyl; specific examples include amino, methylamino, dimethylamino and ethylamino, with amino and methylamino being particularly preferred.

While R_7 has the definitions set forth above, R_7 is preferably hydrogen or optionally substituted amino, with hydrogen, amino and methylamino being particularly preferred.

R_8 is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably straight-chained or branched C_{1-5}alkyl, e.g., methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl and neopentyl.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 include substituted or unsubstituted phenyl (e.g., phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl), C_{3-7}cycloalkyl, heterocyclic rings (e.g., pyrazyl, furyl, thienyl, pyrrolyl,

imidazolyl and quinolinyl) and halogen, with phenyl, cyclohexyl and thienyl being preferred.

The optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, para-fluorobenzyl, 2-thienylmethyl, 3-indolylmethyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

The alkenyl of the optionally substituted straight-chained or branched C_{2-6}alkenyl as R_9 is preferably vinyl, 2-propenyl, 2-propen-1-yl, 2-buten-1-yl or 2-isobuten-1-yl, with 2-propen-1-yl being more preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C_{2-6}alkenyl as R_9 include phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

The optionally substituted straight-chained or branched C_{2-6}alkenyl as R_9 is preferably 2-propen-1-yl.

The alkynyl of the optionally substituted straight-chained or branched C_{2-6}alkynyl as R_9 is preferably ethynyl, propargyl or 2-butyn-1-yl, with 2-butyn-1-yl being preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C_{2-6}alkynyl as R_9 include halogen, phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

The optionally substituted straight-chained or branched C_{2-6}alkynyl as R_9 is preferably 2-butyn-1-yl.

The C_{3-7}cycloalkyl as R_9 is preferably cyclopentyl or cyclohexyl.

Exemplary substituents of the optionally substituted phenyl as R_9 include hydroxy, amino, methyl, ethyl and halogen. The phenyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted phenyl as R_9 is preferably phenyl.

The C_{3-7}cycloalkyl formed by R_9 and R_{20} is preferably cyclopentyl or cyclohexyl.

While R_9 has the definitions set forth above, R_9 is preferably isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, 2-thienylmethyl, 3-indolylmethyl, phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or cyclohexylmethyl, with isopropyl being particularly preferred.

The straight-chained or branched C_{1-3}alkyl as R_{20} is preferably methyl.

R_{20} is preferably hydrogen.

R_{10} is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} include amino optionally substituted with one or more of the same or different kind of straight-chained or branched C_{1-3}alkyl (e.g., amino, methylamino, dimethylamino and ethylamino), optionally substituted 3- to 7-membered cyclic amino (exemplary substituents of the cyclic amino include hydroxy, amino, carboxyl, carbamoyl and methyl), hydroxy, methoxy,

halogen, carbamoyl, methanesulfonyl, ureide, guanidyl, N'-cyano-N"-methylguanidyl, sulfamoylamino, carbamoylmethylamino and methanesulfonylamino, with amino, hydroxy, carbamoyl, methanesulfonyl, ureide, sulfamoylamino, methanesulfonylamino and carbamoylmethylamino being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl, aminomethyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, guanidylmethyl, sulfamoylaminomethyl or methanesulfonylaminomethyl, with methyl, hydroxymethyl and methanesulfonylmethyl being more preferred.

The alkyl of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} of $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl or tert-butyl, with methyl and ethyl being more preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include optionally substituted straight-chained or branched C_{1-3}alkoxy (exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkoxy include hydroxy, amino, carboxyl and carbamoyl), hydroxy, amino, methylamino, dimethylamino, carbamoyl and methanesulfonyl, with hydroxy, methoxy and methanesulfonyl being preferred.

Examples of the optionally substituted straight-

chained or branched C_{1-4}alkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include methyl, ethyl, propyl, isopropyl, tert-butyl, hydroxymethyl, methoxymethyl, 2-hydroxyethyl, 2-aminoethyl, 2-hydroxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 2-amino-2-methylpropyl and methanesulfonylmethyl, with methyl, ethyl, propyl, isopropyl, tert-butyl, hydroxymethyl, methoxymethyl and methanesulfonylmethyl being preferred.

The C_{3-7}cycloalkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably cyclopropyl.

The straight-chained or branched C_{1-4}alkyloxy as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methoxy.

The straight-chained or branched C_{1-4}alkylsulfonyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methanesulfonyl.

Examples of the heterocyclic ring as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O; specific examples include 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl and triazolyl, with 2-pyridyl being preferred.

The 3- to 7-membered cyclic amine of the optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ as R_{11} include aziridine, azetidine, pyrrolidine, piperidine, piperazine and morpholine, with piperazine and morpholine being preferred. Exemplary substituents of the optionally substituted 3- to 7-membered cyclic amine include hydroxy, amino, carboxyl, alkoxycarbonyl, carbamoyl, methyl,

carboxymethyl, alkoxycarbonylmethyl and methylsulfonyl.

The optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ of $-CO-N(R_{14})R_{15}$ as R_{11} is preferably 4-carboxymethylpiperazine, 4-ethoxycarbonylpiperazine, 4-methylsulfonylpiperazine or morpholine.

The $-CO-N(R_{14})R_{15}$ as R_{11} is preferably carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl and 4-methylsulfonyl-1-piperazinecarbonyl, with carbamoyl and ethylcarbamoyl being more preferred.

Examples of the heterocyclic ring of the optionally substituted heterocyclic ring as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O. Exemplary substituents of the heterocyclic ring include oxo, hydroxy, methyl, ethyl and trifluoromethyl; the heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different. Specific examples of the optionally substituted heterocyclic ring include furyl, thienyl, pyrrolyl, oxazolyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 4-pyrimidinon-2-yl, 6-methyl-4-pyrimidinon-2-yl

and imidazolidine-2,4-dion-5-yl, with 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidino-2-yl being preferred.

While R_{11} has the definitions set forth above, R_{11} is preferably methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidinon-2-yl, with carbamoyl and ethylcarbamoyl being more preferred.

The straight-chained C_{1-4}alkyl as R_{16} of $-OR_{16}$ as R_{12} is preferably methyl.

R_{12} is preferably hydroxy.

The straight-chained or branched C_{1-6}alkyl as R_{13} is preferably straight-chained or branched C_{2-5}alkyl, more preferably branched C_{3-5}alkyl, and most preferably tert-butyl.

The straight-chained or branched C_{2-6}alkenyl as R_{13} is preferably straight-chained or branched C_{3-5}alkenyl and more preferably branched C_{3-5}alkenyl.

The straight-chained or branched C_{2-6}alkynyl as R_{13} is

preferably straight-chained or branched C_{3-5}alkynyl and more preferably branched C_{3-5}alkynyl.

R_{17} in Formula (3) as R_{13} is preferably methyl.

The C_{3-7}cycloalkyl formed by R_{18} and R_{19} in Formula (3) as R_{13} is preferably C_{3-5}cycloalkyl.

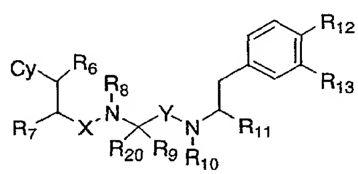
The C_{3-7} cycloalkenyl formed by R_{18} and R_{19} in Formula (3) as R_{13} is preferably C_{3-5}cycloalkenyl.

While R_{13} has the definitions set forth above, R_{13} is preferably isopropyl, tert-butyl, 1,1-dimethylpropyl and 1,1-dimethyl-2-propenyl, with tert-butyl being more preferred.

X is preferably carbonyl or methylene.

Y is preferably carbonyl or methylene.

Examples of compounds of Formula (1)



(1)

wherein:

Cy, R_6, R_7, R_8, R_9, R_{20}, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined as above

include those compounds of which Cy is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy; R_6 is hydrogen or methyl; R_7 is hydrogen or optionally substituted amino; R_8 is hydrogen or methyl; R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or

cyclohexylmethyl; R_{20} is hydrogen; R_{10} is hydrogen or methyl; R_{11} is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl; R_{12} is hydroxy; R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl. More preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea, N-(2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalanynoyl)methylamino]-3-methylbutanamide,

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide, Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-

tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2, N-Me-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)- NH_2, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2SO_2CH_3$, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHcPr and Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHnPr Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHiPr.

Particularly preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, 2-((2-amino-3-(4-

fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide and 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol.

Compounds of Formulae (4) to (10) are useful intermediates for synthesizing the compounds of Formula (1). Various protected functional groups are defined in Formulae (4) to (10); specific examples of protecting groups are shown below:

Examples of the protecting groups of the protected substituent of the straight-chained or branched C_{1-3}alkyl as R_7' include those which are known as useful protecting groups of amino or hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl. Examples of the protecting groups of the protected substituent of the amino as R_7' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl,

trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl. Examples of the protecting groups of the protected hydroxy include those which are known as useful protecting groups of hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched C_{1-3}alkyl as R_{11}" include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected substituent of the straight-chained or branched C_{1-3}alkyl as R_7" include those which are known as useful protecting groups of amino or hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl. Examples of the protecting groups of the optionally protected substituent of the amino as R_7" include those which are

known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl. Examples of the protecting groups of the optionally protected hydroxy as R_7" include those which are known as useful protecting groups of hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of the protected substituent of the straight-chained or branched C_{1-3}alkyl as R_{11}' include those which are known as useful protecting groups of amino or hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of amine as P_1 include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched C_{1-3}alkyl as R_{11}''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P_2 include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Examples of the protecting groups of amine as P_3 include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched C_{1-3}alkyl as R_{11}'''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P_4 include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Examples of the protecting groups of amine as P_5 include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P_6 include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.

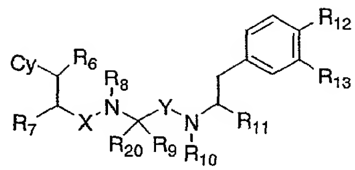
The compounds of the present invention can also be obtained as hydrates.

The subject application claims priority on the basis of Japanese Patent Application Nos. 11-20523 and 11-283163 all disclosures in their specification shall be incorporated herein by reference.

On the pages that follow, the present invention is described more specifically and the amino acids that constitute peptides, the amino acids protected by protecting groups, the protecting groups, reagents and solvents are represented by the following abbreviations: Val: valine, Phe: phenylalanine, Tyr: tyrosine, Z: benzyloxycarbonyl, Boc: tert-butoxycarbonyl, CMPI: 2-chloro-1-methylpyridinium iodide, PyCIU: chloro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluorophosphate, DIC: N,N'-diisopropylcarbodiimide, HOBT: 1-hydroxylbenzotriazole monohydrate, NMM: N-methylmorpholine, TEA: triethylamine, DIEA: diisopropylethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran, DMF: N,N-dimethylformamide, CH: chloroform, MC: methylene chloride, M: methanol, N: concentrated aqueous ammonia, EA: ethyl acetate, H and nHx: n-hexane and ACT: acetone.

BEST MODE FOR CARRYING OUT THE INVENTION

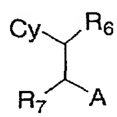
The compounds of Formula (1)



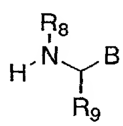
(1)

wherein Cy, R_6, R_7, R_8, R_9, R_{20}, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined above

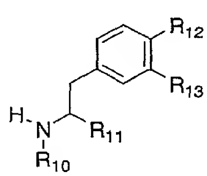
can basically be produced by binding Compound (I), Compound (II) and Compound (III), which are represented by the following formulae and in which functional groups other than those involved in bond formation are protected as required:



(I)



(II)



(III)

A and B in Formulae (I) to (III) are functional groups which can form a bond by the reaction with amino; specific examples are carboxyl, formyl, halomethylene of which halogen is chlorine, bromine or iodine, and sulfonyloxymethylene of which sulfonyl is methanesulfonyl, trifluoromethanesulfonyl, paratoluenesulfonyl and the like. R_1 to R_{10}, R_{12} and R_{13} are as defined above, provided that

when they are reactive groups such as amino, hydroxy or carboxyl, they are protected by normally used appropriate protecting groups, if desired. R_{11} is as defined above or is a functional group which is convertible to one of the above defined groups.

The compounds of Formula (1) may be produced by first binding Compound (II) and Compound (III), optionally followed by deprotection, and then binding the resultant compound with Compound (I), optionally followed by deprotection or conversion of the functional group(s). Alternatively, the compound of Formula (1) may be produced by first binding Compound (I) and Compound (II), optionally followed by deprotection, and then binding the resultant compound with Compound (III), optionally followed by deprotection or conversion of the functional group(s).

The compounds of the present invention may be produced by either the solid-phase process or the liquid-phase process. In the production by the solid-phase process, an automatic organic synthesizer can be used but it may be replaced by the manual procedure.

Almost all amino acids that are used for the production of the compounds of the present invention are commercially available and readily purchasable. Those which are not commercially available can be produced by well-known established methods such as the Strecker synthesis, the Bucherer method, the acetamido malonic ester method, the method of alkylating an amino group protected glycine ester and the Z-α-phosphonoglycine trimethylester

method.

Compound (I), if it has a functional group such as amino and hydroxy, with the functional group being protected, is carboxylic acid (A is $-CO_2H$), aldehyde (A is -CHO), alkylhalide (A is $-CH_2$-Hal), sulfonate (A is $-CH_2-OSO_2R$) or the like. In this case, bond can be formed by reacting A of Compound (I) with the amino group of Compound (II).

Compound (II) can, in almost all cases, be derived from an α-amino acid and B is carboxyl ($-CO_2H$), formyl (-CHO), halomethyl ($-CH_2$-Hal), sulfonyloxymethyl (RSO_2O-CH_2-) or the like. The amino group of Compound (II) is reacted with A of Compound (I) to form bond and B of Compound (II) is reacted with the amino group of Compound (III) to form bond.

Compound (III) is an ethylamine derivative and can be generally derived from an amino acid. The amino group of Compound (III) is reacted with B of Compound (II) to form bond.

When A or B is carboxyl, various methods known in peptide synthesis may be used to activate the carboxyl for condensation with the amino group and such methods include the use of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), the use of PyCIU, the use of bromo tripyrrolidino phosphonium hexafluorophosphate (PyBrop), the use of chlorotripyrrolidino phosphonium hexafluorophosphate (PyClop), the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-

tetramethyluronium hexafluorophosphate (HATU), the use of DIC, the use of N-ethyl-N'-3-dimethylaminopropyl carbodiimide (WSCI), the use of dicyclohexyl carbodiimide (DCC), the use of diphenylphosphorylazide (DPPA), the use of CMPI, the use of 2-bromo-1-methylpyridinium iodide (BMPI), the combination of one of these reagents with HOBT or N-hydroxysuccinimide (HONSu), the mixed acid anhydride method using isobutyl chloroformate or the like, the method of changing the carboxyl group to a pentafluorophenyl ester (OPfp), a p-nitrophenyl ester (ONP) or an N-hydroxysuccinimide ester (OSu), and the combination of one of these methods with HOBT. If necessary, a base such as TEA, DIEA, NMM or 4-dimethylaminopyridine (DMAP) may be added to accelerate the reaction.

When A or B is formyl, bond can be formed by conventional reductive bond forming reaction with amino group. When A or B is halomethylene or sulfonyloxymethylene, bond can be formed by substitution reaction with amino group.

The compounds of the present invention can also be produced by applying the specific methods of production to be described in the following Examples.

On the pages that follow, the production of the compounds of the invention is described more specifically by reference to Examples, to which the invention is by no means limited.

In order to demonstrate the utility of the compounds of the invention, typical examples of them were subjected

to pharmacological tests on the motilin receptor antagonistic action and the results are described under Test Examples. The chemical structural formulae or chemical names of the compounds produced in Examples are set forth in Tables A-1 to A-10 and Tables B-1 to B-18.

Table A-1

Example No.	Structural formula or chemical name
1	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
2	Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
3	Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
4	Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
5	Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
6	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHSO_2Me$ TFAsalt
7	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe
8	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric 2- (3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide
9	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea
10	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine
11	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine
12	2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylsulfamide

Table A-2

Example No.	Structural formula or chemical name
13	2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylaminoacetamide
14	N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2- [N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
15	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide
16	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide
17	2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol
18	(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone
19	2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone
20	5-(1-(2-((2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
21	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

Table A-3

Example No.	Structural formula or chemical name
22	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide
23	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide
24	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide
25	2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

Table A-4

Example No.	Structural formula or chemical name
26	Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
27	Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
28	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2
29	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)- NH_2
30	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)- NH_2
31	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
32	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)- NHMe
33	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)- NHMe
34	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)- NH_2
35	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)- NH_2
36	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
37	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)- NHMe
38	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)- NHMe
39	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2
40	N-Me-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)- NH_2
41	N-Et-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)- NH_2
42	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
43	N-Me-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)- NHMe
44	N-Et-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)- NHMe
45	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2
46	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)- NH_2
47	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)- NH_2
48	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe
49	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)- NHMe
50	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)- NHMe

Table A-5

Example No.	Structural formula or chemical name
51	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH_2
52	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH_2
53	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH_2
54	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe
55	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
56	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
57	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH_2
58	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH_2
59	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH_2
60	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe
61	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
62	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
63	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu
64	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2SO_2CH_3$
65	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
66	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
67	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
68	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide
69	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide
70	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

Table A-6

Example No.	Structural formula or chemical name
71	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
72	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
73	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
74	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
75	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
76	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
77	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-N,3-dimethylbutanamide
78	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Table A-7

Example No.	Structural formula or chemical name
101	Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHEt
102	N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHEt
103	N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHEt
104	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt
105	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt
106	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt
107	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt
108	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt
109	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt
110	Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NHEt
111	N-Me-Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NHEt
112	N-Et -Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NHEt
113	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHEt
114	N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHEt
115	N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NHEt
116	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt
117	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt
118	N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt
119	Phe(4-F)-N-Me-Val- Tyr(3-t Bu)-NH-n-Pr
120	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr
121	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr
122	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH$_2$OH
123	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH$_2$OH
124	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH$_2$OH
125	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH$_2$OH

Table A-8

Example No.	Structural formula or chemical name
126	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH$_2$OH
127	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH$_2$OH
128	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH$_2$OH
129	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH$_2$OH
130	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH$_2$OH
131	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH$_2$OH
132	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH$_2$OH
133	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide
134	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide
135	ethyl 2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl] propanoly)piperazinyl]acetate
136	2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoly)piperazinyl]acetic acid
137	Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH$_2$
138	Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH$_2$
139	Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH$_2$
140	Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH$_2$

Table A-9

Example No.	Structural formula or chemical name
141	Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH_2
142	Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH_2
143	Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH_2
144	Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH_2
145	Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH_2
146	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide
147	(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide
148	Phe(4-F)-N-Me-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2
149	Phe(4-F)-N-Me-D-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2
150	Phe(4-F)-N-Me-Ala(β-CF_3)-N-Me-Tyr(3-tBu)-NH_2
151	Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH_2
152	Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH_2
153	Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH_2
154	Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH_2
155	Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH_2
156	Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH_2
157	Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
158	Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2
159	Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
160	Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2
161	Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH_2
162	Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH_2
163	Phe(4-F)-N-Me-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2

Table A-10

Example No.	Structural formula or chemical name
164	Phe(4-F)-N-Me-D-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2
165	Phe(4-F)-N-Me-Ala(β-c-Pr)-N-Me-Tyr(3-tBu)-NH_2
166	Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH_2
167	Phe(4-F)-N-Me-α-Me-Phe-Tyr(3-tBu)-NH_2
168	Phe(4-F)-N-Me-α-Me-Phe-Tyr(3-tBu)-NH_2
169	Phe(4-F)-N-Me-α-Me-Leu-Tyr(3-tBu)-NH_2
170	Phe(4-F)-N-Me-α-Me-D-Abu-Tyr(3-tBu)-NH_2
171	Phe(4-F)-N-Me-α-Me-D-Val-Tyr(3-tBu)-NH_2
172	(2S)-N-[(N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
173	(2S)-N-[(N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
174	Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH_2
175	Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH_2
176	Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH_2
177	(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
178	(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
179	(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino}-3-methyl-N-methylbutanamide
180	(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpropanoylamino}-3-methyl-N-methyl butanamide
181	Ala(β-4-pyridyl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
182	Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
183	Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

Table B-1

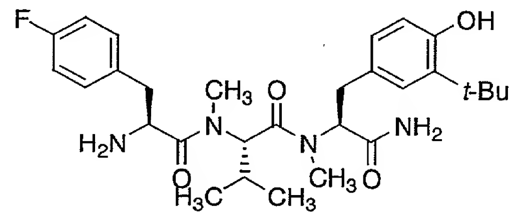
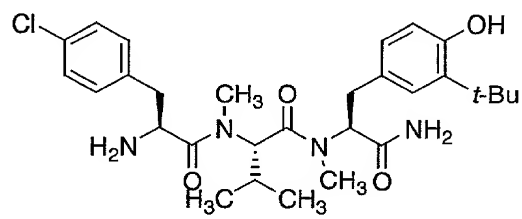
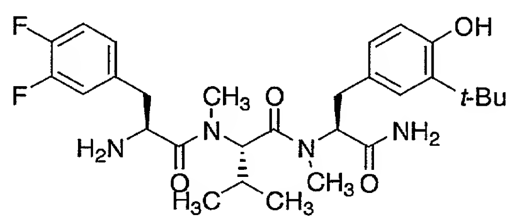
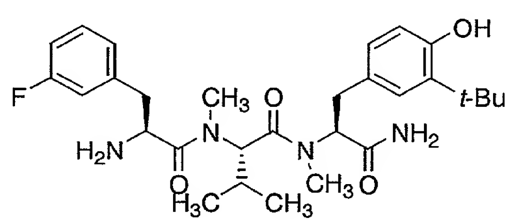
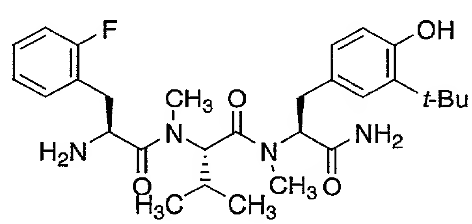
Example No.	Structural formula
1	
2	
3	
4	
5	

Table B-2

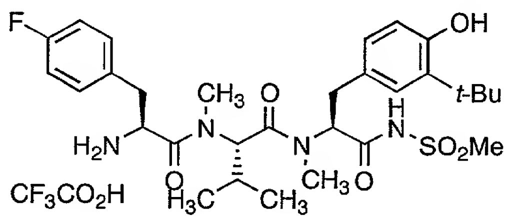
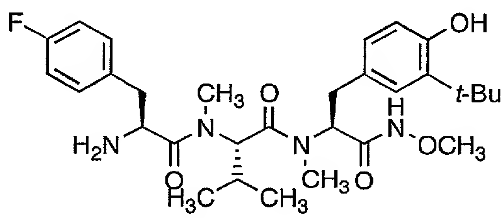
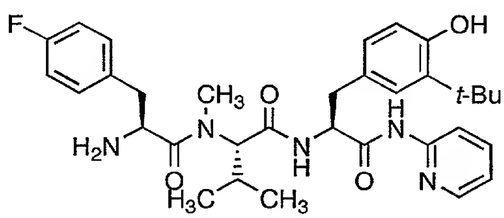
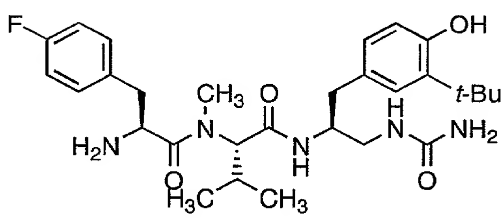
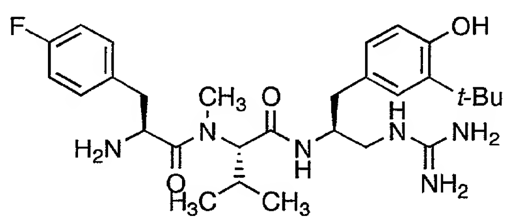
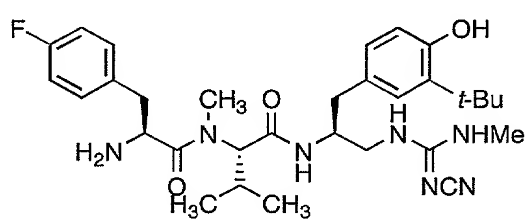
Example No.	Structural formula
6	
7	
8	
9	
10	
11	

Table B-3

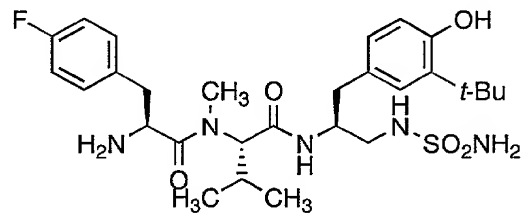
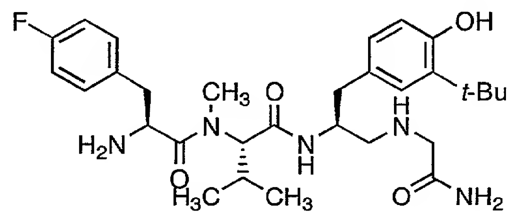
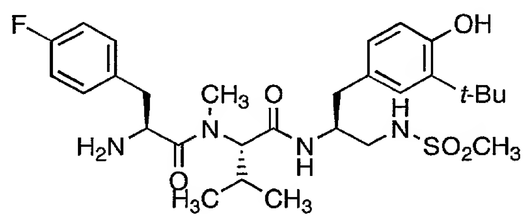
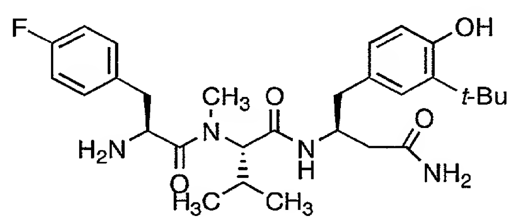
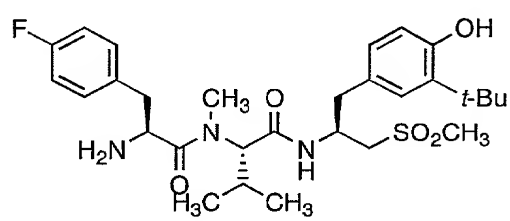
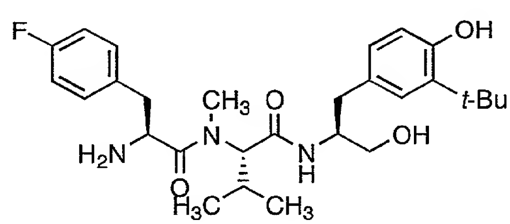
Example No.	Structural formula
12	
13	
14	
15	
16	
17	

Table B-4

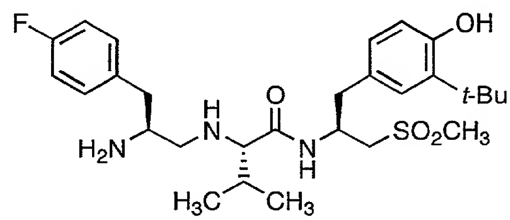
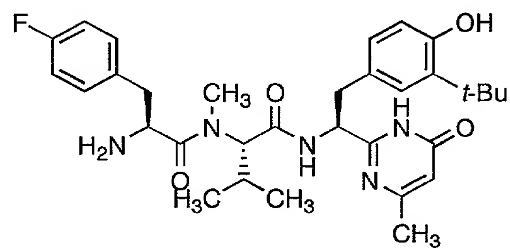
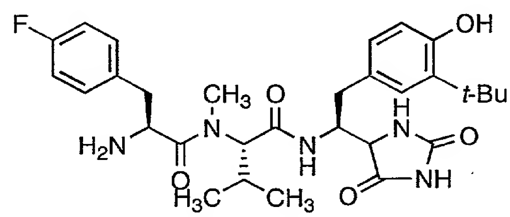
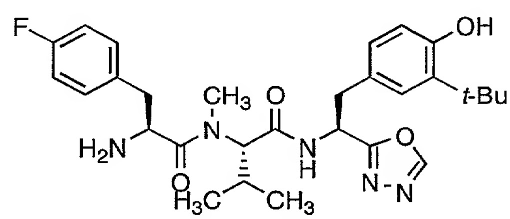
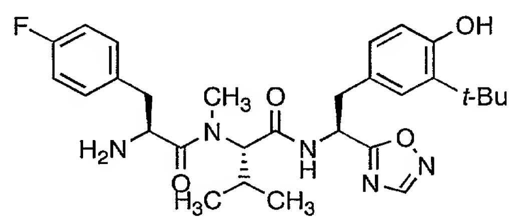
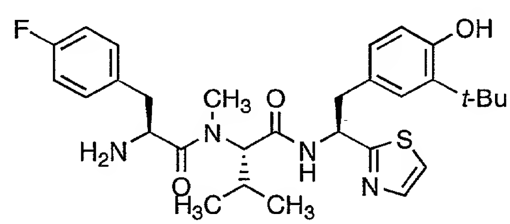
Example No.	Structural formula
18	
19	
20	
21	
22	
23	

Table B-5

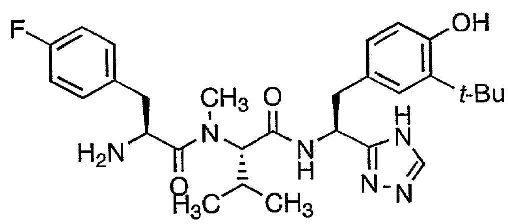
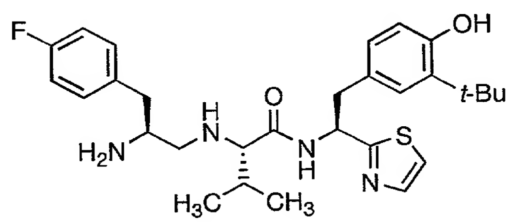
Example No.	Structural formula
24	
25	

Table B-6

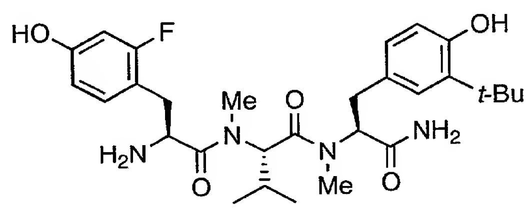
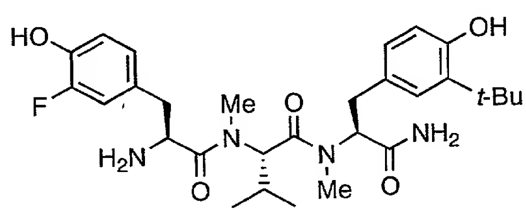
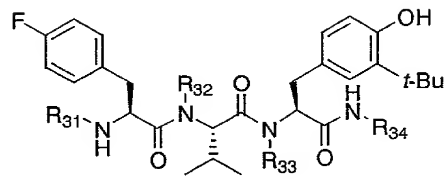
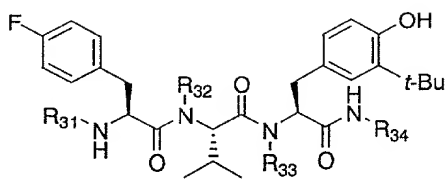
Example No.	Structural formula
26	
27	

Table B-7



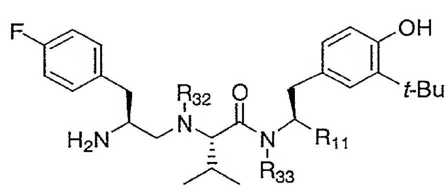
Example No.	R_{31}	R_{32}	R_{33}	R_{34}	Example No.	R_{31}	R_{32}	R_{33}	R_{34}
28	H	Me	H	H	54	H	Et	Me	Me
29	Me	Me	H	H	55	Me	Et	Me	Me
30	Et	Me	H	H	56	Et	Et	Me	Me
31	H	Me	H	Me	57	H	Et	Et	H
32	Me	Me	H	Me	58	Me	Et	Et	H
33	Et	Me	H	Me	59	Et	Et	Et	H
34	Me	Me	Me	H	60	H	Et	Et	Me
35	Et	Me	Me	H	61	Me	Et	Et	Me
36	H	Me	Me	Me	62	Et	Et	Et	Me
37	Me	Me	Me	Me	101	H	Me	H	Et
38	Et	Me	Me	Me	102	Me	Me	H	Et
39	H	Me	Et	H	103	Et	Me	H	Et
40	Me	Me	Et	H	122	H	Me	H	CH_2OH
41	Et	Me	Et	H	123	Me	Me	H	CH_2OH
42	H	Me	Et	Me	124	Et	Me	H	CH_2OH
43	Me	Me	Et	Me	104	H	Me	Me	Et
44	Et	Me	Et	Me	105	Me	Me	Me	Et
45	H	Et	H	H	106	Et	Me	Me	Et
46	Me	Et	H	H	132	H	Me	Me	CH_2OH
47	Et	Et	H	H	125	Me	Me	Me	CH_2OH
48	H	Et	H	Me	126	Et	Me	Me	CH_2OH
49	Me	Et	H	Me	107	H	Me	Et	Et
50	Et	Et	H	Me	108	Me	Me	Et	Et
51	H	Et	Me	H	109	Et	Me	Et	Et
52	Me	Et	Me	H	127	H	Me	Et	CH_2OH
53	Et	Et	Me	H	128	Me	Me	Et	CH_2OH
					129	Et	Me	Et	CH_2OH

Table B-8



Example No.	R_{31}	R_{32}	R_{33}	R_{34}
110	H	Et	H	Et
111	Me	Et	H	Et
112	Et	Et	H	Et
113	H	Et	Me	Et
114	Me	Et	Me	Et
115	Et	Et	Me	Et
116	H	Et	Et	Et
117	Me	Et	Et	Et
118	Et	Et	Et	Et
130	H	Et	Et	CH_2OH
131	Me	Et	Et	CH_2OH
121	H	Me	Me	cPr
119	H	Me	H	nPr
120	H	Me	H	iPr
137	H	Me	nPr	H
63	H	Me	H	tBu
64	H	Me	Me	$CH_2SO_2CH_3$

Table B-9



Example No.	R_{32}	R_{33}	R_{11}	Example No.	R_{32}	R_{33}	R_{11}
65	H	Me	$CONH_2$	72	Me	Me	Me
66	Me	Me	$CONH_2$	73	Ac	Me	Me
67	Ac	Me	$CONH_2$	74	H	H	Me
68	H	Et	$CONH_2$	75	Me	H	Me
69	H	H	CH_2OH	76	Ac	H	Me
70	Me	H	CH_2OH	77	Me	Me	CH_2OH
71	H	Me	Me	78	Me	H	CH_2NH_2

Table B-10

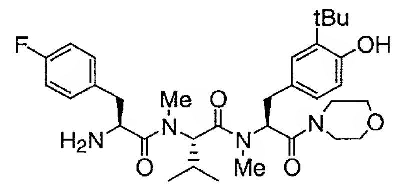
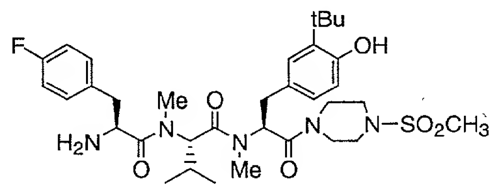
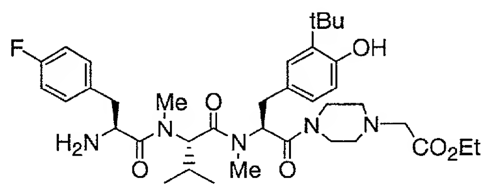
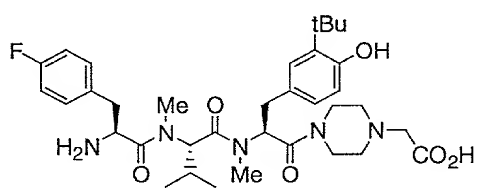
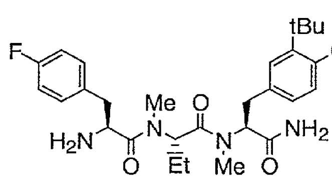
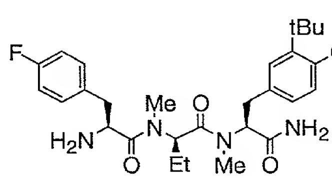
Example No.	Structural formula
133	
134	
135	
136	
138	
139	

Table B-11

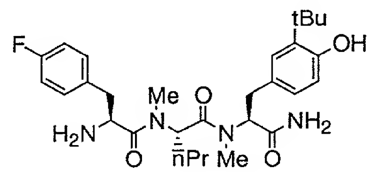
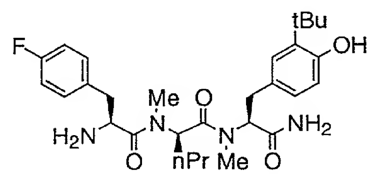
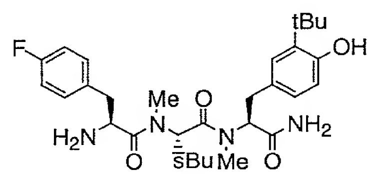
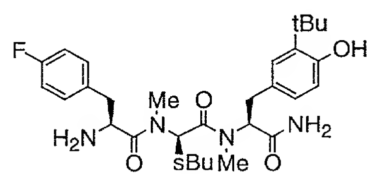
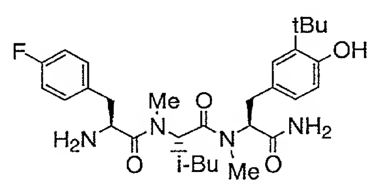
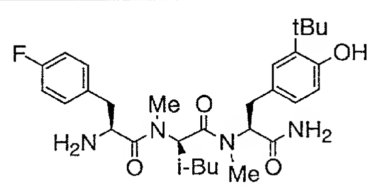
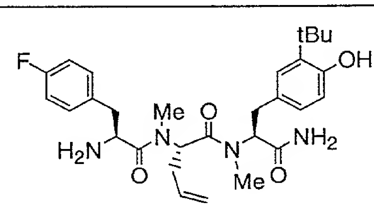
Example No.	Structural formula
140	
141	
142	
143	
144	
145	
146	

Table B-12

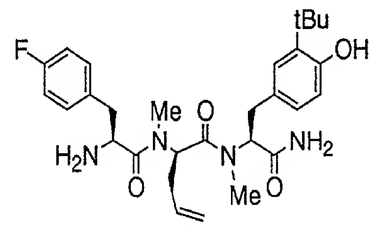
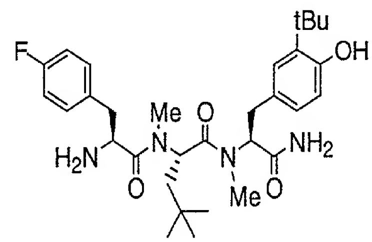
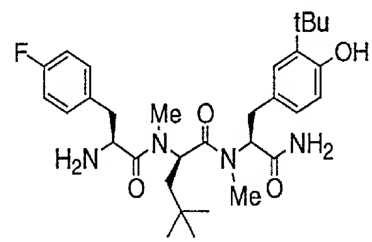
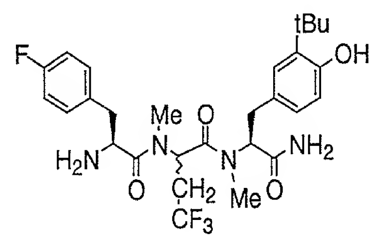
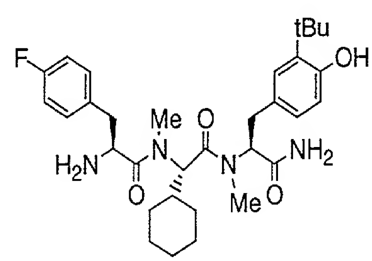
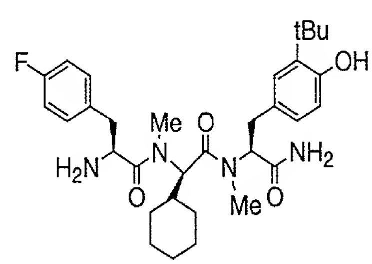
Example No.	Structural formula
147	
148	
149	
150A, 150B	
151	
152	

Table B-13

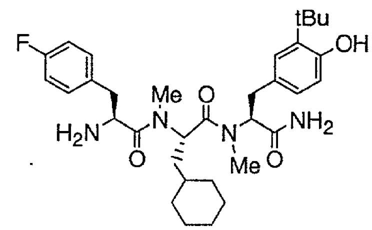
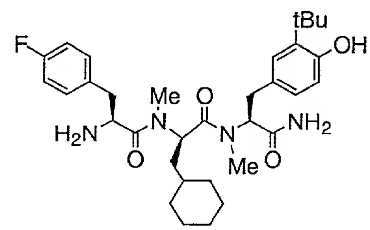
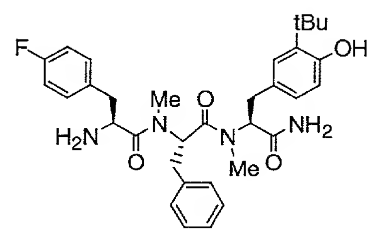
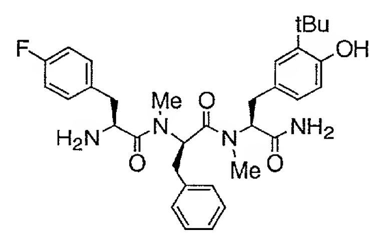
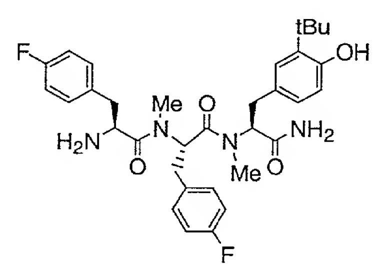
Example No.	Structural formula
153	
154	
155	
156	
157	

Table B-14

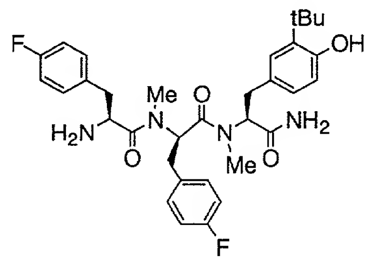
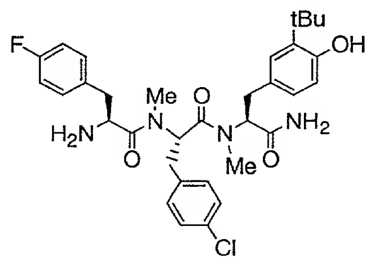
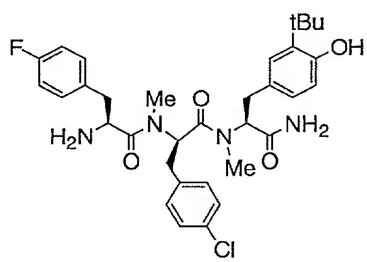
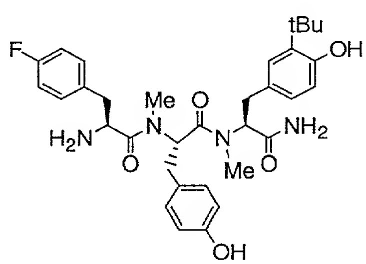
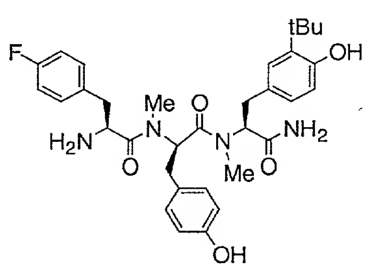
Example No.	Structural formula
158	
159	
160	
161	
162	

Table B-15

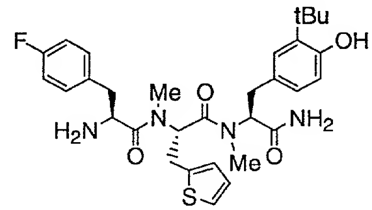
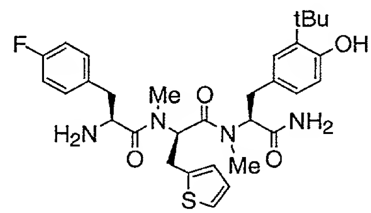
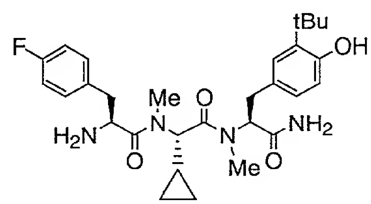
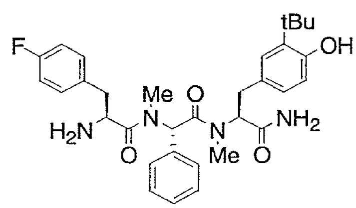
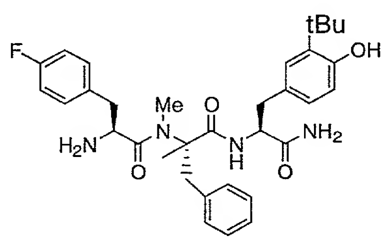
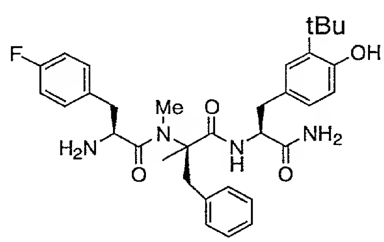
Example No.	Structural formula
163	
164	
165	
166	
167	
168	

Table B-16

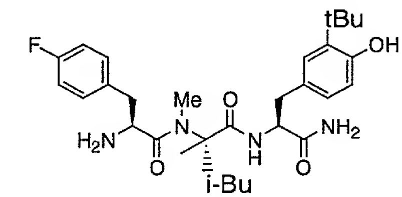
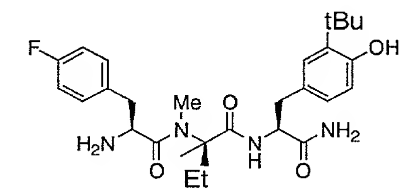
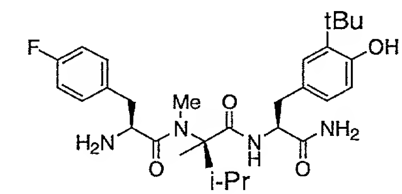
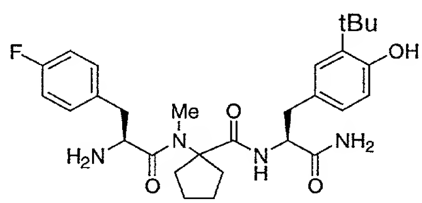
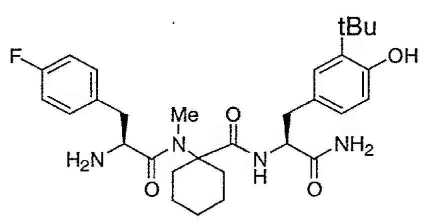
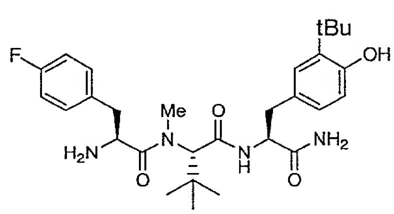
Example No.	Structural formula
169	
170	
171	
172	
173	
174	

Table B-17

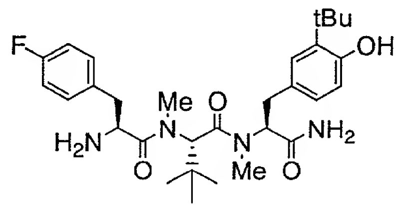
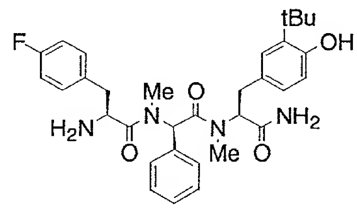
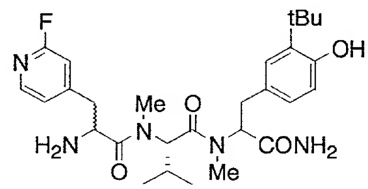
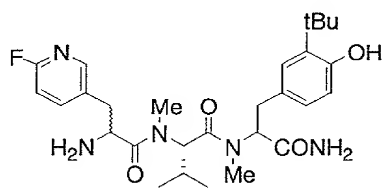
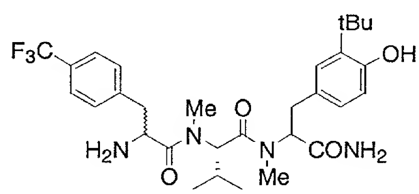
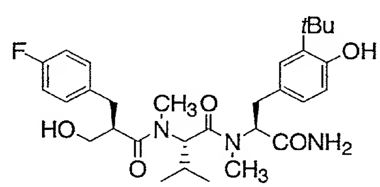
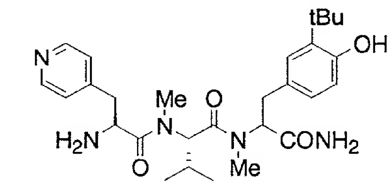
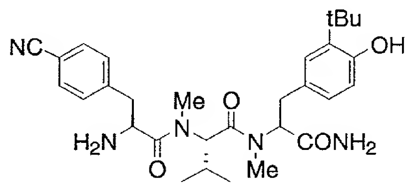
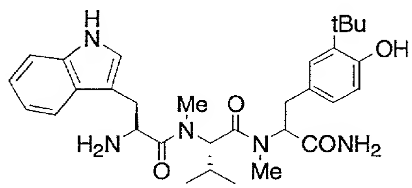
Example No.	Structural formula
175	
176	
177A, 177B	
178A, 178B	
179A, 179B	
180A, 180B	

Table B-18

Example No.	Structural formula
181	
182	
183	

In the following Examples, Merck Silica gel 60 (0.063-0.200 mm) or Merck Silica gel 60 (0.040-0.063 mm) was used for silica gel column chromatography unless otherwise stated.

In the following examples, mass spectra (MA) and ^{1}H-NMR were taken by the following equipment:

MA (EI-MS): SHIMADZU GCMS-QP5050A or SHIMADZU GCMS-QP1000.

MA (ESI-MS): Extrel ELQ400

MA (FAB-MS): JASCO 70-250SEQ

^{1}H-NMR: JEOL JNM-EX-270 (270 MHz) or Bruker ARX300 (300 MHz)

Reaction conditions, data from the equipment, yielded amount and the like of Example 28 onward were shown in Tables in which "Reaction time" means stirring time and "Column sol." means the eluting solvent for silica gel column chromatography.

In the following Examples, the retention time (min.) on HPLC is measured under the following conditions:

Apparatus: HITACHI L-6300 or Young Lin M930

Column: μBONDASPHERE 5μ C18 100A (3.9×150 mm)

Detecting conditions: linear gradient of B (10-80%) using A (0.1% TFA/distilled water) and B (0.1% TFA/acetonitrile), 35 min., flow of rate 1 ml/min, detected at 280 nm (UV).

Example 1

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of Tyr-OMe·HCl (500 g, 2.16 mol) in

tert-butyl acetate (4500 ml), 70% $HClO_4$ (278 ml, 3.24 mol) was added and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was dissolved in ethyl acetate, poured into a saturated aqueous $NaHCO_3$ solution and stirred. The organic layer was collected and washed with a saturated aqueous $NaHCO_3$ solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with ether (950 ml) and at room temperature, stirred overnight. The thus precipitated crystals were collected by filtration to give Tyr(3-tBu)-OMe (242 g, 45%).

^{1}H-NMR($CDCl_3$): δ 1.38(9H,s), 2.83(1H,dd,J=13.7,7.4Hz), 3.02(1H,dd,J=13.7,5.1Hz), 3.70(1H,dd,J=7.4,5.1Hz), 3.73(3H,s), 6.55(1H,d,J=7.9Hz), 6.85(1H,dd,J=7.9,1.7Hz), 7.04(1H,d,J=1.7Hz)

(2) Synthesis of Z-Tyr(3-t-Bu)-OMe

To a solution of Tyr(3-tBu)-OMe (41.4 g, 0.165 mol) in 1,4-dioxane (170 ml) and H_2O (170 ml), under cooling with ice, sodium carbonate (26.2 g, 0.247 mol) was added and then Z-Cl (24.7 ml 0.173 mol) was further added over 25 min., followed by stirring for 2.5 hours at room temperature. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus precipitated crystals were collected by filtration, washed with n-hexane and dried to give Z-Tyr(3-t-Bu)-OMe (54.7 g, 86%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz), 3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s), 5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz), 6.78(1H,dd,J=7.9,2.0Hz), 6.95(1H,d,J=2.0Hz), 7.26-7.41(5H,m)

(3) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

A solution of Z-Tyr(3-tBu)-OMe (1.0 g, 2.60 mmol), benzyl bromide (0.56 ml, 4.68 mmol) and potassium carbonate (1.08 g, 7.79 mmol) in DMSO (5 ml) was stirred overnight. The resulting mixture was mixed with a saturated aqueous ammonium chloride solution, extracted with ethyl acetate. The organic layer was washed with water and then saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 99%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.05(2H,d,J=5.6Hz), 3.71(3H,s), 4.60-4.68(1H,m), 5.06(2H,s), 5.09(2H,s), 5.24(1H,brd,J=8.3Hz), 6.82(1H,d,J=8.5Hz), 6.88(1H,dd,J=8.5,1.8Hz), 7.00(1H,d,J=1.8Hz), 7.27-7.50(10H,m)

(4) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 2.60 mmol) in 1,4-dioxane (30 ml), a 2N aqueous sodium hydroxide solution (3 ml) was added and stirred for 2 hours. The resulting mixture was mixed with water and washed with

ethyl acetate; the aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g).

To a solution of the thus obtained crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g) in THF (7 ml), under cooling with ice, methyl iodide (1.3 ml, 20.8 mmol) was added and then sodium hydride (60% in oil, 312 mg, 7.8 mmol) was added slowly, followed by stirring for 21 hours at room temperature. The resulting mixture was mixed with water, rendered acidic by the addition of dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g).

To a solution of the thus obtained crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g) in THF (25 ml), under cooling with ice, ethyl chloroformate (0.27 ml, 2.86 mmol) and NMM (0.31 ml, 2.86 mmol) were added in that order. The mixture was stirred for 15 min. and further stirred for another 15 min. while bubbling gaseous ammonia therein. The resultant mixture was left standing at room temperature, diluted with ethyl acetate and washed with water and then saturated brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 88%, in 3 steps).

^{1}H-NMR($CDCl_3$): δ 1.37(9H,s), 2.87(3H,s), 2.86-2.99(1H,m), 3.21-3.35(1H,m), 4.73-4.95(1H,m), 5.06(2H,s), 5.09(2H,s), 5.67,5.83 and 6.13(3/2H,brs), 6.78-7.47(27/2H,m)

(5) Synthesis of N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 2.28 mmol) in methanol (20 ml), 10% palladium/carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 96%).

^{1}H-NMR($CDCl_3$): δ 1.40(9H,s), 2.31(3H,s), 2.63(1H,dd,J=14.7,10.7Hz), 3.10-3.19(2H,m), 5.24(1H,brs), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=7.9,1.8Hz), 7.05(1H,brs), 7.10(1H,d,J=1.8Hz)

(6) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Val-OH (700 mg, 2.64 mmol), N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 2.20 mmol) and CMPI (674 mg 2.64 mmol) in THF (22 ml), under cooling with ice, TEA (0.61 ml) was added and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 3:2) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 90%).

^{1}H-NMR($CDCl_3$):(four rotamers) δ 0.07, 0.32, 0.63, 0.74, 0.79, 0.81, 0.84 and 0.89(6H,d,J=6.3-6.6Hz), 1.30, 1.33, 1.37 and 1.39(9H,s), 2.13-2.33(1H,m), 2.34, 2.41, 2.78, 2.87 and 2.98(6H,s), 2.79-3.22(2H,m), 4.40 and 4.32(1H,d,J=10.6Hz), 4.60-5.43(5H,m), 5.96(1H,brs), 6.23-7.12(3H,m), 7.26-7.47(5H,m)

(7) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (Intermediate I-b3 in the following Tables)

A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 1.97 mmol) and 20% palladium hydroxide/carbon (0.10 g) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 1.5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.71 g, 99%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.35,0.71,0.92 and 0.96(6H,d,J=6.9Hz), 1.36 and 1.37(9H,s), 1.73-1.81 and 2.03-2.17(1H,m), 1.74 and 2.23(3H,s), 2.64(1H,d,J=9.2Hz), 2.90-3.04(1H,m), 2.93 and 3.00(3H,s), 3.19 and 4.60(1H,dd,J=14.7,5.8 and 10.7,3.8Hz), 5.29,5.32 and

6.06(2H,brs), 5.59(1H,dd,J=10.4,5.8Hz), 6.54 and 6.60(1H,d,J=7.9Hz), 6.79 and 6.93(1H,dd,J=7.9,2.0 and 1.7Hz), 7.01 and 7.07(1H,d,J=2.0 and 1.7Hz), 8.10(1H,brs)

(8) Synthesis of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-Phe(4-F)-OH (1.09 g, 3.44 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.04 g, 2.87 mmol) and CMPI (878 mg, 3.44 mmol) in THF (30 ml), TEA (0.96 ml, 6.88 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate =1:3) to give Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 91%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.57,0.73,0.75 and 0.90(6H,d,J=6.3-6.6Hz), 1.33 and 1.39(9H,s), 2.18-3.43(5H,m), 2.40 and 3.03(3H,s), 2.74 and 3.01(3H,s), 4.62-5.49(7H,m), 5.95(1H,brs), 6.44(1H,d,J=7.9Hz), 6.57-7.35(12H,m)

(9) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

A mixture of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 2.61 mmol) and 10% palladium/carbon (340 mg) in methanol (50 ml) was stirred at room temperature in a hydrogen atmosphere for 17 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica

gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.25 g, 91%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.50,0.76,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.39(9H,s), 2.19-2.95(5H,m), 2.50 and 3.03(3H,s), 2.81 and 3.02(3H,s), 3.17 and 3.34(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.66 and 3.84(1H,dd,J=8.9,4.6 and 8.6,4.6Hz), 4.91 and 5.07(1H,d,J=10.6Hz), 5.07,5.19,5.30,5.98 and 6.64(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.35 and 6.62(1H,d,J=7.9Hz), 6.74(2/3H,dd,J=7.9,1.7Hz), 6.95-7.11(19/3H,m)

Example 2

Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-OH (354 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.05) to give Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g,

77%).

(2) Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g, 0.697 mmol) in methylene chloride (4 ml), TFA (3 ml) was added, stirred for 20 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with a saturated aqueous $NaHCO_3$ solution, and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 30:1:0.1) to give Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (355 mg, 93%).

EI-MS:544 and 546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.49,0.75,0.78 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.38(9H,s), 2.10-2.92(5H,m), 2.50 and 3.04(3H,s), 2.80 and 3.01(3H,s), 3.13 and 3.33(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.67 and 3.85(1H,dd,J=8.9,5.0 and 8.6,5.0Hz), 4.90 and 5.06(1H,d,J=10.6Hz), 5.33,5.41, 5.99 and 6.61(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.37 and 6.63(1H,d,J=7.9Hz), 6.72 and 6.98(1H,dd,J=7.9,1.7Hz), 7.07-7.10(3H,m), 7.25-7.31(2H,m)

Example 3

Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-

NH_2

To a solution of Fmoc-Phe(3,4-F_2)-OH (500 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05), giving Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.56 g, 80%).

(2) Synthesis of Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 0.715 mmol) in methylene chloride (5 ml), diethylamine (5 ml) was added, stirred for 4 hours and then evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:ethanol:aqueous ammonia = 60:1:0.1) to give Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (381 mg, 97%).

EI-MS:546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.74,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.33 and 1.38(9H,s), 2.10-2.93(5H,m), 2.51 and 3.03(3H,s), 2.83 and 3.01(3H,s), 3.17 and 3.33(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.66 and

3.84(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.07(1H,d,J=10.6Hz), 5.41, 5.9(1H,brs), 5.41-5.51(1H,m), 6.43 and 6.64(1H,d,J=7.9Hz), 6.75(2/5H,dd,J=7.9,1.7Hz), 6.84-7.16(28/5H,m)

Example 4

Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous

magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (241 mg, 87%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.73,0.78 and 0.93(6H,d,J=6.3-6.6Hz), 1.33 and 1.38(9H,s), 2.10-2.96(5H,m), 2.46 and 3.03(3H,s), 2.78 and 3.01(3H,s), 3.16 and 3.35(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.70 and 3.90(1H,dd,J=8.3,5.6 and 8.6,5.0Hz), 4.89 and 5.06(1H,d,J=10.6Hz), 5.42, 5.99(1H,brs), 5.43-5.52(1H,m), 6.41 and 6.64(1H,d,J=7.9Hz), 6.72(2/5H,dd,J=7.9,1.7Hz), 6.83-6.99(18/5H,m), 7.10(2/5H,d,J=1.7Hz), 7.22-7.33(1H,m)

Example 5

Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing

solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (235 mg, 85%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.45,0.71,0.79 and 0.93(6H,d,J=5.9-6.6Hz), 1.31 and 1.38(9H,s), 2.10-2.89(5H,m), 2.47 and 3.06(3H,s), 2.76 and 3.01(3H,s), 3.14 and 3.34(1H,dd,J=14.3,5.9 and 13.9,6.6Hz), 3.79 and 3.95(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.06(1H,d,J=10.6Hz), 5.37, 5.99(1H,brs), 5.41-5.51(1H,m), 6.43(3/5H,d,J=7.9Hz), 6.56(2/5H,brs), 6.60-6.71(1H,m), 6.92-7.29(6H,m)

Example 6

TFA salt of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHSO_2Me$

(1) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-$NHSO_2Me$

To a solution of crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (0.95 g, 2.0 mmol), WSCI·HCl (0.77 g, 3.99 mmol) and methanesulfonamide (0.29 g, 3.0 mmol) in DMF (15 ml), DMAP (0.49 g, 0.99 mmol) was added under cooling with ice and stirred at room temperature overnight. The mixture was mixed with water and then with 2N hydrochloric acid, extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give the titled compound (0.83 g, 75%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 2.80(s,3H), 2.97-3.30(m,2H), 3.21(s,3H), 4.60-4.74(m,1H), 5.08(s,2H), 5.13(s,2H), 6.81(d,1H,J=8.2Hz), 6.86-7.13(m,2H), 7.20-7.46(m,10H), 9.0(brs,1H)

(2) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$

A mixture of Z-N-Me-Tyr(3-tBu-4-benzyloxy)-$NHSO_2Me$ (0.80 g, 1.45 mmol) and 20% palladium hydroxide/carbon (0.09 g) in methanol (15 ml) was stirred at room temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.53 g).

To a solution of the crude N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.51 g, 1.43 mmol), Z-N-Me-Val-OH 0.49 g, 1.86 mmol) and CMPI (0.51 g, 2.00 mmol) in THF (10 ml), TEA (0.60 ml, 4.29

mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water, rendered acidic by the addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 0.5% acetic acid) to give the titled compound (0.70 g, in 2 steps, 85%).

(3) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$

A mixture of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.65 g, 1.13 mmol) and 20% palladium hydroxide/carbon (0.09 g) in methanol (10 ml) was stirred at room temperature for 2.5 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.50 g).

To a solution of the above crude compound (0.48 g, 1.09 mmol), Boc-Phe(4-F)-OH 0.40 g, 1.41 mmol) and CMPI (0.39 g, 1.53 mmol) in THF (8 ml), TEA (0.46 ml, 3.27 mmol) was added under cooling with ice and stirred at room temperature overnight for 22 hours. The reaction mixture was mixed with water, rendered acidic by the addition of 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 5% acetic acid) to give the titled compound (0.50 g, in 2 steps, 65%).

(4) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ TFA salt

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (208 mg, 0.294 mmol) in methylene chloride (6 ml), TFA (3 ml) was added and stirred for 1.5 hours. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was dissolved in a mixture of acetonitrile/water (1:10) (80 ml), which mixture containing 0.1% TFA, and lyophilized to give the titled compound (0.20 g, 94%).

EI-MS:606(M^+)

^1H-NMR(DMSO-d_6):(three rotamers) δ 0.02(d,3/5H,J=5.9Hz), 0.22(d,3/5H,J=5.9Hz), 0.62(d,3/5H,J=7.6Hz), 0.68(d,3/5H,J=6.6Hz), 0.77(d,9/5H,J=6.6Hz), 0.89(d,9/5H,J=6.3Hz), 1.28(s,27/5H), 1.31(s,9/5H), 1.35(s,9/6H), 1.86-2.03(m,2/7H), 2.15-2.28(m,5/7H), 2.5-3.4(m,10H), 4.35-4.62(m,1H), 4.80-5.02(1H), 5.11-5.42(m,1H), 6.55-7.18(m,7H), 8.0-8.2(m,3H), 8.98-9.06(m,1H), 11.2(brs,1H)

Example 7

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

(1) Synthesis of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe

To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-OH (3.8 g, 7.99 mmol) in THF (50 ml), ethyl chloroformate (0.85 ml, 8.78 mmol) was added under cooling with ice and then NMM (0.97 ml, 8.78 mmol) was slowly added dropwise. After stirring for 1 hour, $MeONH_2$ (1.0 g, 12.0 mmol) and TEA 2.23 ml (16.0 mmol) were added to the mixture, followed by stirring for 2 hours at room temperature. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2) to give the titled compound (2.7 g, 67%).

^{1}H-NMR($CDCl_3$): δ 1.39(9H,s), 2.95(3H,s), 2.99(1H,m), 3.24(1H,m), 3.64(3H,s), 4.7(1H,m), 5.1(4H,d), 6.8-7.5(13H,m), 9.06(1H,s)

(2) Synthesis of N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe (2.7 g, 5.36 mmol) in MeOH (30 ml), palladium hydroxide /carbon (675 mg) was added and stirred in a hydrogen atmosphere for 2 hours. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1) to give the titled compound (1.24 g, 82%).

^{1}H-NMR($CDCl_3$): δ 1.43(9H,s), 2.45(3H,s), 2.92(2H,m), 3.12(1H,m), 3.59(3H,s), 6.77(1H,d,J=9.4Hz),

6.95(1H,dd,J=2.8,3.4Hz), 7.13(1H,d,J=3.15Hz)

(3) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of N-Me-Tyr(3-tBu)-NHOMe (1.24 g, 4.42 mmol), Z-N-Me-Val-OH (1.76 g, 6.63 mmol) and CMPI (1.7 g, 6.63 mmol) in THF (30 ml), TEA (1.23 ml, 8.84 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1) to give the titled compound (1.32 g, 57%).

^{1}H-NMR($CDCl_3$): δ 0.43(3H,m), 0.80(3H,m), 1.36(9H,s), 3.02(9H,m), 3.65(3H,s), 4.4(1H,m), 5.1(3H,m), 6.4-7.4(8H,m)

(4) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (1.23 g, 2.33 mmol) in MeOH (20 ml), palladium hydroxide/carbon (350 mg) was added and stirred in a hydrogen atmosphere for 1 hour. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure to give crude N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (0.91 g).

A solution of the thus obtained crude compound (0.98 g, 2.5 mmol), Boc-Phe(4-F)-OH (0.92 g, 3.25 mmol) and CMPI (0.83 g, 3.25 mmol) in THF 20 ml, TEA (0.52 ml, 3.75 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic

layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (972 mg, 56%).

(6) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (972 mg, 1.508 mmol) in methylene chloride (10 ml), TFA (7 ml) was added and stirred for 30 min. The mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (288 mg, 34%).

EI-MS:558(M^+)

^{1}H-NMR($CDCl_3$): δ 0.42(3H,d,J=13.5Hz), 0.79(3H,d,J=13.2Hz), 1.33(9H,s), 2.10(1H,m), 2.60(1H,m), 2.90(2H,m), 2.91(3H,s), 3.07(3H,s), 3.28(1H,m), 3.68(3H,s), 3.91(1H,m), 4.82(1H,d,J=10.7Hz), 5.13(1H,m), 6.60(1H,d,J=10.4Hz), 6.89(1H,m), 7.0-7.3(5H,m), 9.1(1H,m)

Example 8

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of Z-Tyr(3-tBu)-OH (3.04 g, 8.19 mmol)

in THF (8.2 ml), under cooling with ice N,N-carbonyldiimidazole (1.59 g, 9.83 mmol) was added and stirred for 1 hour. To the mixture, 2-aminopyridine (925 mg, 9.83 mmol) was then added and stirred for 2 hours under cooling with ice and then further 6.5 hours at room temperature. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.16 g, 59%).

^{1}H-NMR($CDCl_3$): δ 1.24(9H,s), 2.95-3.20(2H,m), 4.45-4.60(1H,m), 5.11(2H,dd,J=17.5,12.2Hz), 6.53(1H,d,J=7.9Hz), 6.85(1H,d,J=7.9Hz), 6.95-7.15(2H,m), 7.32(5H,brs), 7.67-7.73(1H,m), 8.15-8.25(2H,m)

(2) Synthesis of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (2.16 g, 4.83 mmol) in methanol (160 ml), 10% palladium/carbon (400 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 10:1:100), giving the titled compound (1.48 g, 98%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 2.72-3.23(2H,m), 3.67-3.72(1H,m), 6.62(1H,d,J=7.9Hz), 6.85-6.88(1H,m), 6.95-7.20(2H,m), 7.70-7.77(1H,m), 8.29-8.39(2H,m)

(3) Synthesis of 2-(N-benzyloxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (1.48 g, 4.73 mmol), Z-N-Me-Val-OH (1.63 g, 6.15 mmol) and CMPI (1.57 g, 6.15 mmol) in THF 30 ml, TEA (1.5 ml, 10.88 mmol) was added under cooling with ice and stirred for 3 hours under cooling with ice. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.74 g, 65%).

^{1}H-NMR($CDCl_3$): δ 0.70-0.95(6H,m), 1.26(9H,s), 2.20-2.35(1H,m), 2.70-3.10(5H,m), 4.00-4.20(1H,m), 4.65-4.80(1H,m), 5.17(2H,brs), 6.44(1H,d,J=7.6Hz), 6.60-6.85(1H,m), 6.95-7.10(2H,m), 7.36(5H,brs), 7.60-7.75(1H,m), 8.10-8.25(2H,m)

(4) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 2-(N-benzyloxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-

hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.74 g, 3.10 mmol) in methanol (50 ml), 10% palladium carbon (300 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 5:0.1:100), giving the titled compound (1.30 g, 98%).

^{1}H-NMR($CDCl_3$): δ 0.69(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.31(9H,s), 1.95-2.11(1H,m), 2.36(3H,s), 2.81(1H,d,J=4.6Hz), 2.99-3.18(2H,m), 4.73-4.81(1H,m), 6.59(1H,d,J=7.9Hz), 6.94(1H,dd,J=7.9,2.0Hz), 7.00-7.10(2H,m), 7.65-7.72(1H,m), 7.80(1H,d,J=7.9Hz), 8.18(1H,d,J=8.6Hz), 8.25(1H,d,J=4.6Hz),

(5) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.25 g, 2.93 mmol), Boc-Phe(4-F)-OH (1.08 g, 3.81 mmol) and CMPI (973 mg, 3.81 mmol) in THF 19 ml, TEA (0.94 ml, 6.74 mmol) was added under cooling with ice and stirred for 4 hours under cooling with ice. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure;

the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.72 g, 85%).

^{1}H-NMR($CDCl_3$): δ 0.65-1.02(6H,m), 1.26(9H,s), 1.34(9H,s), 2.20-2.40(1H,m), 2.75-3.15(4H,m), 2.89(3H,s), 4.20-4.35(1H,m), 4.70-5.00(2H,m), 6.61(1H,d,J=7.9Hz), 6.75-7.20(7H,m), 7.60-7.80(1H,m), 8.20-8.30(2H,m)

(6) 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.67 g, 2.41 mmol) in methylene chloride (30 ml), TFA (5 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was mixed with chloroform, washed with a saturated aqueous $NaHCO_3$ solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (370 mg).

EI-MS:591(M^+)

^{1}H-NMR($CDCl_3$): δ 0.74(2H,d,J=6.9Hz), 0.77(1H,d,J=6.9Hz), 0.88(1H,d,J=6.3Hz), 0.95(2H,d,J=6.3Hz), 1.25(9H,s), 2.24-

2.44(1H,m), 2.50-3.25(4H,m), 2.78(2.4H,s), 2.85(0.6H,s), 3.55-3.65(0.8H,m), 3.80-3.90(0.2H,m), 4.00(0.8H,d,J=10.9Hz), 4.36(0.2H,d,J=10.9Hz), 4.65-4.80(0.2H,m), 4.90-5.00(0.8H,m), 6.55-7.20(8H,m), 7.65-7.75(1H,m), 8.15-8.25(2H,m)

Example 9

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

(1) Synthesis of Z-3-tBu-tyrosinol

To a solution of Z-Tyr(3-tBu)-OMe (7.4 g, 19 mmol) in THF (190 ml), lithium borohydride (1.25 g, 57.4 mmol) was added under cooling with ice and stirred for 1.5 hours at room temperature. The mixture was mixed with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (6.8 g, 99%).

^{1}H-NMR($CDCl_3$): δ 1.38(9H,s), 2.15(1H,m), 2.78(2H,brd,J=6.9Hz), 3.5-3.8(2H,m), 3.8-4.0(1H,m), 4.86(1H,s), 4.9-5.0(1H,m), 5.09(2H,s), 6.58(1H,d,J=7.9Hz), 6.88(1H,brd,J=7.9Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of Z-3-tBu-tyrosinol (2 g, 5.6 mmol),

triphenylphosphine (1.76 g, 6.7 mmol), phthalimide (0.99 g, 6.7 mmol) in THF 50 ml, diethyl azodicarboxylate (DEAD) (1.05 ml, 6.7 mmol) was added under cooling with ice and stirred at the same temperature for 1 hour. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1) to give (1-(1,3-dihydro-1,3-dioxo-isoindol-2-yl)methyl-2-(3-tBu-4-hydroxyphenyl)ethyl)carbamic acid benzyl ester (3.2 g).

To the above compound (3.2 g), a 40% methylamine methanol solution (40 ml) was added at room temperature and stirred at the same temperature for 10 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (1.9 g).

^{1}H-NMR($CDCl_3$): δ 1.37(9H,s), 2.6-2.9(4H,m), 3.7-3.9(4/5H,m), 3.9-4.1(1/5H,m)4.8-4.9(4/5H,m), 5.09(2H,s), 5.4-5.5(1/5H,m), 6.5-6.6(1H,m), 6.84(1H,d,J=7.3Hz), 6.9-7.1(1H,m), 7.33(5H,s)

(3) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

A mixture of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (1.0 g, 2.8 mmol), potassium

cyanate (0.5 g, 5.5 mmol), acetic acid (0.5 ml), dioxane (10 ml) and water (10 ml) was stirred at 60°C for 2 hours. The mixture was mixed with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:methanol = 50:1), giving the titled compound (0.9 g, 80%).

^{1}H-NMR(CD_3OD): δ 1.35(9H,s), 2.5-2.8(2H,m), 3.0-3.2(1H,m), 3.2-3.4(1H,m), 3.7-3.9(1H,m), 5.01(2H,d,J=3.6Hz), 6.63(1H,d,7.9Hz), 6.84(1H,brd,J=7.9Hz), 7.04(1H,brs), 7.2-7.4(5H,m)

(4) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.9 g, 2.26 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.54 g).

To a solution of the above compound (0.53 g, 2 mmol), Z-N-Me-Val-OH (0.69 g, 2.6 mmol) and CMPI (0.67 g, 2.6 mmol) in THF (20 ml), TEA (1 ml, 7.2 mmol) was added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.98 g, 98%).

^{1}H-NMR($CDCl_3$): δ 0.82(3H,d,J=6.3Hz), 0.88(3H,d,J=6.3Hz), 1.35(9H,s), 2.1-2.3(1H,m), 2.6-2.8(2H,m), 2.76(3H,s), 3.0-3.4(2H,m), 3.9-4.1(1H,m), 4.7-5.0(2H,m), 5.0-5.1(2H,m), 5.5-5.6(1H,m), 6.4-7.0(5H,m), 7.34(5H,s)

(5) Synthesis of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.97 g, 1.95 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure, giving N-(2-(2-amino-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.72 g).

To a solution of the above crude compound (0.64 g, 1.85 mmol), Boc-Phe(4-F)-OH (0.63 g, 2.22 mmol) and CMPI (0.57 g, 2.23 mmol) in THF (18 ml), TEA (0.93 ml, 6.67 mmol) was added under cooling with ice and stirred at room temperature for 8 hours. The mixture was mixed with water

and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.79 g, 66%).

^{1}H-NMR(DMSO-d_6): δ 0.70, 0.75, 0.85, and 0.95(total 6H,d,J=5.9-6.3Hz), 1.2-1.4(18H,m), 2.0-2.1(1H, m), 2.4-2.9(7H,m), 2.9-3.1(2H,m), 3.8-4.0(1H,m), 4.3-4.6(2H,m), 5.39, 5.51(2H,brs), 5.74(1H,d,J=1.3Hz), 5.9-6.0(1H,m), 6.6-6.9(2H,m), 6.9-7.1(2H,m), 7.1-7.3(3H,m), 7.60 and 7.73(total 1H, brd), 9.02(1H,s)

(6) Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.75 g) in methylene chloride (6 ml), TFA (6 ml) was added under cooling with ice, stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent:

chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (480 mg, 76%).

FAB-MS:544(M^{+}+1)

^{1}H-NMR(DMSO-d_6): δ 0.49, 0.73, and 0.85(total 6H,d,J=6.0-6.6Hz), 1.30 and 1.32(total 9H,s), 2.0-2.2(1H,m), 2.4-3.1(9H,m), 3.7-4.1(3H,m), 4.52 and 5.48(total 2H,m), 5.8-6.0(1H,m), 6.6-6.8(2H,m), 6.9-7.3(5H,m), 7.67 and 8.79(total 1H,d,J=7.6-8.6Hz), 9.01 and 9.06(total 1H,s)

Example 10

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

(1) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)amine (1.46 g, 4.1 mmol) in dioxane (8 ml), an aqueous sodium carbonate solution (0.44 g, 4.1 mmol) (8 ml) and $(Boc)_2O$ (0.9 g, 4.1 mmol) were added in that order under cooling with ice and stirred at the same temperature for 2.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.7 g, 91%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 1.42(9H,s), 2.6-2.9(2H,m), 3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.7-4.8(1H,m), 5.08(2H,s), 6.58(1H,d,J=8.9Hz), 6.85(1H,brd,J=8.9Hz), 7.03(1H,brs), 7.2-7.5(5H,m)

(2) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.6 g, 3.5 mmol) in methanol (35 ml), 10% palladium carbon (160 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1.5 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-((2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.1 g).

To a solution of the thus obtained crude compound (1.1 g, 3.42 mmol), Z-N-Me-Val-OH (1.08 g, 4.08 mmol) and CMPI (1.04 g, 4.07 mmol) in THF (35 ml), TEA (1.7 ml, 12.2 mmol) was added under cooling with ice and stirred at room temperature for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.8 g, 93%).

^{1}H-NMR($CDCl_3$):δ 0.82(3H,d,J=6.6Hz), 0.90(3H,d,J=6.2Hz), 1.37(9H,s), 1.42(9H,s), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.0-

3.3(2H,m), 3.9-4.3(2H,m), 5.13(2H,s), 6.44(1H,d,J=7.9Hz), 6.75(1H,brd,J=7.9Hz), 7.00(1H,brs), 7.36(5H,s)

(3) Synthesis of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.8 g, 3.16 mmol) in methanol (35 ml), 10% palladium carbon (180 mg) was added and stirred for 1 hour in a hydrogen atmosphere at room temperature. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-(2-(N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.33 g).

To a solution of the thus obtained crude compound (1.33 g, 3.15 mmol), Z-Phe(4-F)-OH (1.2 g, 3.78 mmol) and CMPI (0.97 g, 3.78 mmol) in THF (35 ml), TEA (1.6 ml, 11.5 mmol) was added under cooling with ice and stirred at room temperature for 10 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.48 g, 53%).

^{1}H-NMR($CDCl_3$):δ 0.68, 0.75, 0.91, and 0.98(total 6H,d,J=6.2-6.9Hz), 1.35,1.37,1.40, and 1.42(total 18H,m),

2.1-3.4(10H,m), 4.0-4.5, 4.7-5.1, and 5.5-5.7(total 7H,m), 6.3-7.5(17H, m)

(4) Synthesis of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.38 g) in methylene chloride (5 ml), TFA (5 ml) was added under cooling with ice, stirred at room temperature for 30 min. and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (1.1 g, 92%).

^{1}H-NMR($CDCl_3$):δ 0.67,0.76,0.92,and 0.97(total 6H,d,J=6.6-6.9Hz), 1.35 and 1.37(total 9H,s), 2.2-2.5(1H,m), 2.4-3.1(9H,m), 4.0-4.2 and 4.4-4.5(total 2H,m), 4.7-5.1(2H,m), 5.5-5.6 and 5.7-5.9(total 1H,brd,J=7.6-8.1Hz), 6.2-6.4, 6.5-6.7, and 6.8-7.4(total 13H,m)

(5) Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (580 mg, 0.91 mmol) in DMF (4.5 ml), 1H-pyrazole-1-carboxamidine hydrochloride (161 mg, 1.09 mmol) and DIEA (0.19 ml, 1.09 mmol) were added at room temperature and stirred at the same temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 100:1 to 10:1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine (410 mg).

To a solution of the above compound (410 mg) in methanol (20 ml), 10% palladium carbon (40 mg) was added and stirred in a hydrogen atmosphere at room temperature for 5 hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol =5:1), giving the titled compound (250 mg, 76%).

FAB-MS:543(M^{+}+1)

^{1}H-NMR(CD_3OD)):δ 0.47, 0.53, 0.80, 0.90(6H,d,J=6.3-6.9Hz), 1.31, 1.37(9H,s), 2.0-2.3(1H,m), 2.41, 2.46, and 2.57(total

3H,s), 2.5-3.4(6H,m), 3.8-4.6(3H,m), 6.6-7.3(7H,m)

Example 11

Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (500 mg, 0.79 mmol) in ethanol (4 ml), dimethyl N-cyanodithioiminocarbonate (127 mg, 0.87 mmol) was added at room temperature and stirred at the same temperature for 16 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was mixed with a 40% methylamine methanol solution (5 ml) at room temperature and stirred at the same temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine (450 mg).

To a solution of the above compound (440 mg) in methanol (6 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 15

hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (280 mg, 78%).

FAB-MS:582(M^{+}+1)

^{1}H-NMR($CDCl_3$):δ 0.62, 0.79, 0.87, and 0.91(total 6H,d,J=6.3-6.6Hz), 1.37 and 1.40(total 9H,s), 2.1-2.4(1H,m), 2.5-3.0(10H,m), 3.1-3.4(2H,m), 3.6-4.4(3H,m), 5.8-6.1(1H,m), 6.6-7.2(7H,m), 8.68(1H,d,J=6.6Hz)

Example 12

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (514 mg, 0.811 mmol) in 1,4-dioxane (8 ml), sulfamide (156 mg, 1.62 mmol) was added and stirred at 120°C for 5 hours. The reaction mixture was evaporated under reduced pressure to remove the solvent; the thus obtained residue was mixed with water, and extracted with chloroform. The organic layer was washed

with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (397 mg, 69%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.69,0.85 and 0.99(6H,d,J=6.3-6.6Hz), 1.36 and 1.37(9H,s), 1.80-1.90(1H,m), 2.22-2.40(1H,m), 2.43 and 2.81(3H,s), 2.60-3.10(4H,m), 3.26-3.38(1H,m), 3.70-3.80(1H,m), 3.90-4.10(1H,m),4.28-4.44(1H,m), 4.72-5.30(3H,m), 5.03(2H,s), 6.52-6.66(2H,m), 6.80-7.40(10H,m)

(2) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

A mixture of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide (332 mg, 0.466 mmol) and 10% palladium carbon (40 mg) in methanol (5 ml) was stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 200:10:1), giving the titled compound (180 mg, 67%).

FAB-MS:580(M+H$^+$)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.63,0.75,0.81 and

0.93(6H,d,J=6.3-6.6Hz), 1.38 and 1.39(9H,s), 2.20-3.42(6H,m), 2.60 and 3.02(3H,s), 3.49(1H,s), 3.60-3.90(2H,m), 4.30-4.44(1H,m), 5.30-5.40(1H,m), 6.56-7.16(7H,m), 8.34-8.42(1H,m)

Example 13

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (1.17 g, 1.84 mmol) in ethanol (18 ml), ethyl glyoxylate (0.7 ml, 2.76 mmol), acetic acid (1.8 ml) and sodium cyanoborohydride (173 mg, 2.76 mmol) were added and stirred for 1 hour. The reaction mixture was mixed with a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate:methylene chloride = 2:3:1), giving the titled compound (900 mg, 68%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.65,0.75,0.91 and 0.97(6H,d,J=6.2-6.9Hz), 1.22 and 1.29(3H,t,J=7.2Hz), 1.35 and 1.36(9H,s), 2.22-2.40(1H,m), 2.42 and 2.90(3H,s), 2.60-3.02(5H,m), 3.22-3.46(2H,m), 4.06-4.28(2H,m), 4.47(1H,d,J=12.2Hz), 4.80-5.12(3H,m), 5.29(2H,s), 5.74(1H,d,J=8.9Hz), 6.58-7.42(12H,m)

(2) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester (889 mg, 1.23 mmol) in methanol (24 ml), aqueous ammonia (16 ml) was added and stirred for 15 hours at room temperature. The reaction mixture was evaporated to remove the solvent under reduced pressure, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 110:10:1), giving the titled compound (600 mg, 70%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.65,0.75,0.90 and 0.96(6H,d,J=6.0-6.6Hz), 1.36 and 1.37(9H,s), 2.22-2.40(1H,m), 2.47 and 2.82(3H,s), 2.60-3.02(4H,m), 3.24 and 3.26(2H,s), 4.02-4.38(2H,m), 4.76-5.08(3H,m), 5.40-

5.90(3H,m), 6.56-7.38(12H,m)

(3) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide (595 mg, 0.860 mmol) in methanol (10 ml), 20% palladium hydroxide/carbon (150 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol:hexane = 10:1:1), giving the titled compound (333 mg, 70%).

FAB-MS:558($M+H^+$)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.66,0.79 and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.39(9H,s), 2.22-2.38(1H,m), 2.63 and 2.91(3H,s), 2.50-2.82(4H,m), 3.12-3.28(2H,m), 3.58-3.88(2H,m), 4.18-4.40(2H,m), 5.50-5.70(1H,m), 6.58-7.14(8H,m)

Example 14

N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide

(1) Synthesis of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine

To a solution of Z-Phe(4-benzyloxy-3-tBu)-OMe (5.8 g, 12.2 mmol) in methanol/water (100 ml/20 ml), sodium borohydride (1.5 g, 36.6 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (5.1 g, 94%).

(2) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine

To a solution of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine (5.09 g, 11.4 mmol), triphenylphosphine (4.41 g, 17.1 mmol) and phthalimide (2.51 g, 17.1 mmol) in THF (66 ml), diethyl azodicarboxylate (3.0 ml, 17.1 mmol) was added and stirred for 4 hours under cooling with ice. The reaction mixture was concentrated; a solution of the thus obtained residue in methanol (70 ml) was mixed with hydrazine (6 ml) and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent:

methylene chloride:methanol = 10:1), giving the titled compound (2.45 g, 49%).

(3) N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide

To a solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine (1.27 g, 2.84 mmol) in methylene chloride (29 ml), TEA (0.6 ml, 4.26 mmol) and then methanesulfonyl chloride (0.3 ml, 3.69 mmol) were added slowly under cooling with ice. After stirring for 30 min., the mixture was mixed with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:1:2), giving the titled compound (1.23 g, 83%).

(4) Synthesis of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide (1.2 g, 2.29 mmol) was dissolved in a mixture of methanol (23 ml) and methylene chloride (5 ml), mixed with palladium hydroxide/carbon (0.60g) and stirred for 12 hours in a hydrogen atmosphere. After filtering off insoluble material using Celite, the filtrate was concentrated to give crude N-[2-amino-3-(4-benzyloxy-3-tert-butylphenyl)propyl]methanesulfonamide (0.68 g).

^{1}H-NMR($CDCl_3$):δ 1.39(s,9H), 2.48(dd,1H,J=8.2,13.9Hz), 2.73(dd,1H,J=5.1,13.3Hz), 2.94(dd,1H,J=7.9,11.9Hz), 2.96(s,3H), 3.10-3.22(m,1H), 3.24(dd,1H,J=3.6,12.2Hz), 6.60(d,1H,J=7.9Hz), 6.83(dd,1H,J=2.0,7.9Hz), 7.03(d,1H,J=2.0Hz)

To a solution of the above crude compound (0.66 g), Z-N-Me-Val-OH (758 mg, 2.86 mmol) and CMPI (730 mg, 2.86 mmol) in THF (22 ml), TEA (0.91 ml, 6.59 mmol) was added under cooling with ice. The resultant was stirred overnight at room temperature, mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled compound (1.08 g, 90%).

(5) Synthesis of 2-[N-(N-benzyloxycarbonyl-4-fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

To a solution of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide (1.0 g, 1.83 mmol) in methanol (18 ml), palladium hydroxide/carbon (0.40 g) was added and stirred in a hydrogen atmosphere for 1.5 hours. After filtering off insoluble material using Celite, the filtrate was

concentrated; to a solution of the thus obtained residue (0.75 g), Z-Phe(4-F)-OH (748 mg, 2.66 mmol) and CMPI (602 mg, 2.36 mmol) in THF 18 ml, TEA (0.82 ml, 5.44 mmol) was added under cooling with ice. The mixture was stirred at room temperature overnight, mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled compound (827 mg, 64%).

(6) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide

To a solution of 2-[N-(N-benzyloxycarbonyl-4-fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide (680 mg, 0.95 mmol) in methanol (10 ml), palladium hydroxide/carbon (0.25 g) was added and stirred in a hydrogen atmosphere for 1 hour. After filtering off insoluble material using Celite, the filtrate was concentrated; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 100:10:1), giving the titled compound (494 mg, 89%).

EI-MS:578(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.62(d,21/10H,J=6.9Hz),

0.75(d,9/10H,J=6.6Hz), 0.84(d,9/10H,J=6.6Hz), 0.93(d,21/10H,J=6.3Hz), 1.36(s,27/10H), 1.39(s,63/10H), 2.20-2.45(m,1H), 2.46-2.95(m,8H), 3.02-3.17(m,3H), 3.61-4.05(m,2H), 4.18-4.37(m,1H), 4.87-4.95(m,7/10H), 5.23-5.35(m,3/10H), 5.55-5.70(m,3/10H), 6.20-6.50(m,7/10H), 6.60-7.20(m,7H), 8.01(d,1H,J=7.6Hz)

Example 15

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethyl carbamic acid benzyl ester

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (2.46 g, 5.19 mmol) in THF (50 ml), lithium borohydride (339 mg, 15.57 mmol) was added under cooling with ice and stirred at room temperature for 3 hours. The reaction mixture was mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.30 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.11(1H,brs), 2.80(2H,d,J=6.9Hz), 3.54-3.77(2H,m), 3.83-3.97(1H,m), 4.88-4.97(1H,m), 5.09(4H,s), 6.85(1H,d,J=8.3Hz),

6.97(1H,dd,J=8.3,1.8Hz), 7.11(1H,d,J=1.8Hz), 7.27-7.50(10H,m)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (1.87 g, 4.18 mmol) in pyridine (42 ml), methanesulfonyl chloride (0.36 ml, 4.60 mmol) was added under cooling with ice. After stirring for 1 hour, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving the titled compound (1.93 g, 88%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.76-2.92(2H,m), 2.96(3H,s), 4.10-4.21(2H,m), 4.21-4.32(1H,m), 4.88-5.00(1H,m), 5.09(4H,s), 6.86(1H,d,J=8.6Hz), 6.98(1H,brd,J=7.9Hz), 7.11(1H,brs), 7.30-7.48(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester 1.93 g, 4.23 mmol) in DMSO (11 ml), potassium cyanide (827 mg, 12.7 mmol) was added and heated at 70°C. After stirring for 4 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.42 g, 74%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.46(1H,dd,J=16.8,4.0Hz), 2.74(1H,dd,J=16.8,4.6Hz), 2.82(1H,dd,J=13.8,8.4Hz), 2.96(1H,dd,J=13.8,6.5Hz), 4.07-4.18(1H,m), 4.89-4.98(1H,m), 5.09(4H,s), 6.87(1H,d,J=8.3Hz), 6.99(1H,dd,J=8.3,1.5Hz), 7.12(1H,d,J=1.5Hz), 7.36-7.47(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine

To a solution of 2-(4-benzyloxy-3-tbutylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

A mixture of the above crude compound, 20% palladium hydroxide/carbon (0.50 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (639 mg, 84%).

^{1}H-NMR(DMSO):δ 1.33(9H,s), 1.96(1H,dd,J=14.5,8.6Hz), 2.12(1H,dd,J=14.5,4.0Hz), 2.37(1H,dd,J=13.4,7.4Hz),

2.46-2.55(1H,m), 3.07-3.20(1H,m), 6.68(1H,d,J=8.2Hz), 6.73(1H,brs), 6.79(1H,brd,J=8.2Hz), 7.40(1H,brs), 9.05(1H,s)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-N-Me-Val-OH (736 mg, 2.78 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine (579 mg, 2.32 mmol) and CMPI (710 mg, 2.78 mmol) in THF (23 ml), TEA (0.77 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving the titled compound (1.09 g, 95%).

^{1}H-NMR($CDCl_3$):δ 0.78-0.90(6H,m), 1.37(9H,s), 2.14-2.80(5H,m), 2.72(3H,s), 3.92-4.04(1H,m), 4.32-4.48(1H,m), 5.04,5.15(2H,brs), 5.27-5.37(1H,m), 5.78,6.03(1H,brs), 6.38-6.82(3H,m), 7.04(1H,brs), 7.30-7.41(5H,m).

(6) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.04 g, 2.09 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and

stirred in a hydrogen atmosphere at room temperature for 1 hour. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.67 g, 88%).

^{1}H-NMR($CDCl_3$):δ 0.68(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.82-1.97(1H,m), 2.27(3H,s), 2.45(1H,dd,J=15.8,7.3Hz), 2.68(1H,d,J=4.6Hz), 2.78-2.91(2H,m), 4.41-4.56(1H,m), 5.30(1H,brs), 5.58(1H,brs), 6.34(1H,brs), 6.62(1H,d,J=8.0Hz), 6.92(1H,dd,J=8.0,2.0Hz), 7.04(1H,d,J=2.0Hz), 7.63(1H,brd,J=8.9Hz)

(7) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-Phe(4-F)-OH (650 mg, 2.05 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (0.62 g, 1.71 mmol) and CMPI (524 mg, 2.05 mmol) in THF (17 ml), TEA (0.57 ml, 4.10 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-

N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.05 g, 93%).

A mixture of the above compound (1.16 g, 1.75 mmol) and 10% palladium carbon (120 mg) in methanol (18 ml) was stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (761 mg, 82%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):δ 0.67,0.80,0.90,0.92(6H,d,J=6.3-6.9Hz), 1.37, 1.39(9H,s), 2.21-3.22(6H,m), 2.61,2.89(3H,s), 3.59-3.88,4.34-4.48(3H,m), 5.33,5.42(1H,brs), 5.90,6.07(1H,brs), 6.56-7.18(7H,m), 8.71(1H,brd,J=8.3Hz)

Example 16

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (2.07 g, 4.63 mmol) in pyridine (46 ml), toluenesulfonyl chloride (6.79 g, 35.6 mmol) was added under cooling with ice. After stirring for 6.5 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was

washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.46 g, 88%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 2.42(3H,s), 2.72-2.86(2H,m), 3.92-4.09(3H,m), 4.84-4.95(1H,m), 5.04(2H,s), 5.07(2H,s), 6.79(1H,d,J=8.0Hz), 6.87(1H,brd,J=8.0Hz), 7.06(1H,brs), 7.26-7.48(12H,m), 7.76(2H,d,J=8.3Hz)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester 2.4 g, 3.99 mmol) in ethanol (40 ml), a solution of sodium methanethiolate (560 mg, 7.99 mmol) in methanol (4 ml) was added and stirred at 40°C for 3 hours. The mixture was evaporated under reduced pressure to remove the solvent, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 5:1), giving the titled compound (1.63 g, 86%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.12(3H,s), 2.61(2H,d,J=5.6Hz), 2.85(2H,d,J=6.3Hz), 3.99-4.12(1H,m), 4.80-4.91(1H,m),

5.09(4H,s), 6.85(1H,d,J=8.3Hz), 6.96(1H,brd,J=7.6Hz), 7.11(1H,brs), 7.27-7.50(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester

To a solution of benzyl ester of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid (1.54 g, 3.23 mmol) in THF (75 ml) and water (25 ml), oxone (5.91 g, 6.46 mmol) was added at room temperature. After stirring for 1 hour, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving the titled compound (1.59 g, 97%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.88(3H,brs), 3.00(2H,brd,J=6.9Hz), 3.17(1H,dd,J=14.8,4.6Hz), 4.19-4.30(1H,m), 4.35-4.47(1H,m), 5.07-5.18(1H,m), 5.09(2H,s), 5.10(2H,s), 6.85(1H,d,J=8.5Hz), 6.97(1H,dd,J=8.5,1.7Hz), 7.10(1H,brs), 7.28-7.49(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine

A mixture of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester (1.0 g, 1.96 mmol) and 20% palladium hydroxide/carbon (0.08 g) in methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced

pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.56 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.40(9H,s), 2.64(1H,dd,J=13.7,7.9Hz), 2.73(1H,dd,J=13.7,5.9Hz), 2.93-3.03(1H,m), 2.98(3H,s), 3.13(1H,dd,J=14.2,2.0), 3.61-3.74(1H,m), 6.62(1H,d,J=7.9Hz), 6.88(1H,dd,J=7.9,2.0), 7.05(1H,d,J=2.0Hz)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of Z-N-Me-Val-OH (518 mg, 1.96 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine (0.47 g, 1.63 mmol) and CMPI (500 mg, 1.96 mmol) in THF (16 ml), TEA (0.55 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving the titled compound (0.70 g, 81%).

^{1}H-NMR($CDCl_3$):δ 0.83(3H,d,J=6.6Hz), 0.89(3H,d,J=6.3Hz), 1.38(9H,s), 2.14-2.33(1H,m), 2.64-2.97(2H,m), 2.74(3H,s), 2.91(3H,s), 3.13(1H,dd,J=14.6,4.6Hz), 3.29(1H,dd,J=14.6,6.9Hz), 3.94(1H,d,J=11.2Hz), 4.43-

4.57(1H,m), 4.79(1H,brs), 5.14(2H,s), 6.40-6.84(3H,m), 7.06(1H,brs), 7.37(5H,brs).

(6) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide (0.65 g, 1.22 mmol) in methanol (10 ml), 10% palladium carbon (130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 30 min. After filtration, the filtrate was concentrated under reduced pressure. To a solution of the thus obtained residue, Z-Phe(4-F)-OH (465 mg, 1.47 mmol) and CMPI (375 mg, 1.47 mmol) in THF (15 ml), TEA (0.41 ml, 2.93 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:n-hexane: ethyl acetate =1:1) to give 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide (484 mg, 57%). A mixture of the above compound (424 mg, 0.609 mmol) and 10% palladium carbon (43 mg) in methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere for 2

hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol=15:1), giving the titled compound (239 mg, 70%).

EI-MS:563(M^+)

^{1}H-NMR($CDCl_3$):δ 0.65,0.78,0.91,0.93(6H,d,J=6.6-7.3Hz), 1.38, 1.39(9H,s), 2.22-2.40(1H,m), 2.46-3.40(6H,m), 2.66(3H,s), 2.93(3H,s), 3.60-3.83(1H,m), 3.87,4.26(1H,d,J=10.8Hz), 4.38-4.67(1H,m), 6.57-7.17,8.88(8H,m)

Example 17

Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

(1) Synthesis of 3-tBu-tyrosinol

To a solution of Z-3-tBu-tyrosinol (8.2 g, 23 mmol) in methanol (250 ml), 10% palladium carbon (800 mg) was added and stirred in a hydrogen atmosphere at room temperature for 10 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (5.1 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.40(9H,s), 2.45(1H,dd,J=8.6,13.5Hz), 2.71(1H,dd,5.3,13.5Hz), 3.0-3.2(1H,m), 3.38(1H,dd,J=7.6,10.5Hz), 3.65(1H,dd,J=3.6,10.5Hz), 6.61(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.06(1H,d,J=2.0Hz)

(2) Synthesis of (2-(benzyloxycarbonyl-N-methylamino)-3-

methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 3-tBu-tyrosinol (1 g, 4.48 mmol), Z-N-Me-Val-OH (1.43 g, 5.4 mmol) and CMPI (1.38 g, 5.4 mmol) in THF (45 ml), TEA (2.2 ml, 15.8 mmol) was added under cooling with ice and stirred at room temperature for 13 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 90%).

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.6Hz), 0.92(3H,d,J=6.3Hz), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.5-3.7(2H,m), 3.9-4.2(2H,m), 5.13(2H,s), 6.2-6.4(1H,m), 6.45(1H,d,J=7.6Hz), 6.80(1H,brd,J=7.6Hz), 7.05(1H,brs), 7.36(5H,s)

(3) Synthesis of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of (2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.9 g, 4 mmol) in methanol (40 ml), 10% palladium carbon (190 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.4 g).

To a solution of the above crude compound (1.4 g), Boc-Phe(4-F)-OH (1.4 g, 4.94 mmol) and CMPI (1.3 g, 5.09 mmol) in THF (40 ml), TEA (2 ml, 14.3 mmol) was added under cooling with ice and stirred at room temperature for 12 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 78%).

^{1}H-NMR($CDCl_3$):δ 0.77, 0.92, and 1.02(total 6H,d), 1.2-1.5(18H,m), 2.2-3.1(8H,m), 3.5-3.8(2H,m), 4.0-4.3, 4.4-4.5, 4.7-4.9, and 5.2-5.4(total 2H,m), 6.3-7.5(8H,m)

(4) Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (0.5 g) in methylene chloride (2 ml), TFA (2 ml) was added under cooling with ice, stirred for 1 hour at room temperature and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography

(developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (250 mg, 60%).

EI-MS:501(M^+)

^{1}H-NMR($CDCl_3$):δ 0.68, 0.79, and 0.93(total 6H,d,J=6.3-6.9Hz), 1.36 and 1.39(total 9H,s), 2.2-2.4(1H,s), 2.5-3.2(4H,m), 2.68 and 2.84(total 3H,s), 3.5-3.9(3H,m), 3.89 and 4.43(total 1H,d,J=10.9Hz), 4.0-4.4(1H,m), 6.5-7.1(7H,m), 6.58 and 8.41(total 1H,d,J=6.9-7.6Hz)

Example 18

(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

(1) Synthesis of (2-(2-(benzyloxycarbonylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (797 mg, 1.56 mmol) in methanol (15 ml), 10% palladium hydroxide (80 mg) was added and stirred at room temperature for 12 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (400 mg, 90%).

To a solution of the above crude compound (400 mg, 1.4 mmol), Z-Val-OH (528 mg, 2.1 mmol) and CMPI (539 mg, 2.1 mmol) in THF (10 ml), TEA (0.58 ml, 4.2 mmol) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (504 mg, 69%).

^{1}H-NMR($CDCl_3$):δ 0.79(3H,d,J=6.9Hz), 0.91(3H,d,J=6.6Hz), 1.38(9H,s), 2.0-2.2(1H,m), 2.89(3H,s), 2.97(2H,d,J=6.9Hz), 3.1-3.4(2H,m), 3.94(1H,dd,J=5.6,7.9Hz), 4.4-4.6(1H,m), 5.10(2H,s), 5.1-5.2(1H,m), 5.35(1H,brs), 6.59(1H,d,J=8.3Hz), 6.5-6.7(1H,m), 6.88(1H,brd,J=8.3Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of of (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester

To a solution of Boc-Phe(4-F)-OH (1 g, 3.53 mmol) and O,N-dimethylhydroxylamine hydrochloride (0.38 g, 3.9 mmol) in methylene chloride (17 ml), TEA (1.1 ml, 7.9 mmol) and BOP (1.64 g, 3.7 mmol) were added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving N-methoxy-N-methyl-2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamide (1.08 g, 94%).

To a solution of the above compound (1 g, 3.07 mmol)

in ether (30 ml), lithium aluminum hydride (120 mg, 3.16 mmol) was added at -10°C and stirred at the same temperature for 10 min. The reaction mixture was mixed with 15 ml of a solution of potassium hydrogen sulfate (630 mg, 4.63 mmol). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (0.8 g, 98%).

^{1}H-NMR($CDCl_3$):δ 1.44(9H,s), 3.0-3.2(2H,m), 4.3-4.5(1H,m), 5.02(1H,brs), 7.00(2H,t,J=8.6Hz), 7.13(2H,dd,J=5.4,8.6Hz), 9.63(1H,s)

(3) Synthesis of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(benzyloxycarbonylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (500 mg, 0.96 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(2-amino-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (330 mg).

To a solution of the above crude compound (330 mg, 0.86 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic

acid tBu ester (275 mg, 1.03 mmol) in methanol (8 ml), acetic acid (0.07 ml, 1.22 mmol) and sodium cyanoborohydride (85 mg, 1.29 mmol) were added in that order under cooling with ice and stirred at room temperature for 30 min. The reaction mixture was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1), giving the titled compound (520 mg, 95%).

^{1}H-NMR($CDCl_3$):δ 0.68(3H,d,J=5.6Hz), 0.85(3H,d,J=6.9Hz), 1.38(9H,s), 1.41(9H,s), 1.9-2.1(1H,m), 2.4-2.9(5H,m), 2.9-3.1(2H,m), 2.99(3H,s), 3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.47(1H,d, J=8.9Hz), 4.5-4.8(1H,m), 5.56(1H,brs), 6.64(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.7-7.9(1H,m)

(4) Synthesis of (2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (520 mg) in methylene chloride (2 ml), TFA (2 ml) was added under cooling with ice, stirred at room temperature for 30 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (400 mg, 91%).

EI-MS:535(M^+)

^{1}H-NMR($CDCl_3$):δ 0.75(3H,d,J=6.9Hz), 0.89(3H,d,J=6.9Hz), 1.39(9H,s), 2.0-2.1(1H,m), 2.3-2.5(2H,m), 2.53(1H,dd,J=3.6,11.6Hz), 2.72(1H,dd,J=4.6,13.2Hz), 2.80(1H,d,J=4.6Hz), 2.8-3.1(5H,m), 3.19(2H,d,J=5.9Hz), 4.5-4.7(1H,m),6.62(1H,d,J=7.9Hz), 6.93(1H,dd,J=2.0,7.9Hz), 6.99(2H,t,J=8.8Hz), 7.0-7.2(3H,m), 7.80(1H,d,J=8.6Hz)

Example 19

2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

(1) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropionitrile

To a solution of Z-Phe(4-benzyloxy-3-tBu)-NH_2 (4.6 g, 10 mmol) in THF (20 ml), pyridine (1.6 ml, 20 mmol) and trifluoroacetic anhydride (1.55 ml, 11 mmol) were added under cooling with ice and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:4), giving the titled compound (3.35 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 3.0(2H,m), 4.85(1H,brd), 5.03(1H,brd), 5.10(2H,s), 5.14(2H,s), 6.69(1H,d,J=8.58Hz), 7.05(1H,d,J=8.58Hz)7.2(1H,s), 7.3-7.5(10H,m)

(2) Synthesis of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone

A solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropionitrile (3.48 g, 7.85 mmol) in saturated hydrochloric acid/ethanol (50 ml) was stirred at room temperature for 1.5 days. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was dissolved in ethanol (70 ml); into the thus obtained solution, gaseous ammonia was blown under cooling with ice, followed by stirring at room temperature for 17 hours. The resultant was concentrated under reduced pressure; the thus obtained residue was dissolved in methanol (50 ml), mixed with methyl acetoacetate (0.640 ml) and potassium hydroxide (562 mg) and stirred at room temperature for 4.5 days. The mixture was mixed with a saturated aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.76 g, 67%).

^{1}H-NMR($CDCl_3$):δ 1.39(9H,s), 2.25(3H,s), 3.09(2H,brd), 4.89(1H,brd), 5.03(2H,s), 5.07(2H,s), 5.80(1H,brd), 6.14(1H,s), 6.79(1H,d,J=8.24Hz), 6.92(1H,d,J=8.24Hz),

6.96(1H,s), 7.25-7.43(10H,m)

(3) Synthesis of 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone

A suspension of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone (1.76 g, 3.35 mmol) and 20% palladium hydroxide/carbon (0.15 g) in methanol (30 ml) was stirred in a hydrogen atmosphere for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (824 mg, 82%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 2.32(3H,s), 2.74(1H,dd,J=8.90,9.24Hz), 3.15(1H,dd,J=4.28,4.29Hz), 4.09(1H,m), 6.16(1H,s), 6.59(1H,d,J=7.92Hz), 6.83(1H,d,J=7.92Hz), 6.99(1H,s).

(4) Synthesis of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

To a solution of Z-N-Me-Val-OH (678 mg, 2.55 mmol), 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone (700 mg, 2.32 mmol) and CMPI (653 mg, 2.55 mmol) in THF (20 ml), TEA (0.97 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove

the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (0.77 g, 61%).

^{1}H-NMR($CDCl_3$):δ 0.79-0.90(6H,m), 1.30(9H,m), 2.2(4H,m), 2.8-3.1(5H,m), 4.3(1H,d,J=7.3), 4.97(1H,m), 5.1-5.25(2H,m), 6.18(1H,d,J=8.58), 6.41(1H,d,J=8.58Hz), 6.5-6.85(2H,m), 7.3(5H,m)

(5) Synthesis of 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone

A mixture of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (0.71 g, 1.294 mmol), 20% palladium hydroxide/carbon (0.15 g) and methanol (20 ml) was stirred in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving two diastereoisomers A and B of the titled compound, A (296 mg, 38%) being eluted first and then B (77 mg, 9.4%).

(A)

^{1}H-NMR($CDCl_3$):δ 0.72(3H,d,J=6.93Hz), 0.83(3H,d,J=6.93Hz), 1.34(9H,s), 1.94(1H,m), 2.28(3H,s), 2.30(3H,s), 2.77(1H,d,J=4.62Hz), 3.11(2H,m), 5.04(1H,d,J=7.59Hz), 6.14(1H,s), 6.61(1H,d,J=7.92Hz), 6.81(1H,dd,J=7.92Hz), 6.99(1H,s), 7.84(1H,d,J=6.92Hz)

(B)

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.93Hz), 0.89(3H,d,J=6.93Hz), 1.33(9H,s), 2.00(1H,m), 2.14(3H,s), 2.18(3H,s), 2.78(1H,d,J=4.95Hz), 3.11(2H,m), 5.10(1H,d,J=6.60Hz), 6.14(1H,s), 6.63(1H,d,J=7.92Hz), 6.75(1H,dd,J=7.92Hz), 6.97(1H,s), 7.81(1H,d,J=7.26Hz)

(6) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of Boc-Phe(4-F)-OH (200 mg, 0.707 mmol), 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (A) (244 mg, 0.589 mmol) and CMPI (180 mg, 0.706 mmol) in THF (8 ml), TEA (0.25 ml, 4.7 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving the titled compound (0.33 g, 82%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.75, 0.80 and 0.98(6H,d,J=6.6,6.9Hz), 1.34 and 1.38(9H,s), 1.4 (9H,s), 2.10(1H,m), 2.3 and 2.4(3H,s), 2.7(3H,s), 2.85(2H,m), 3.04(2H,d,J=7.01Hz), 4.12 and 4.58(1H,d,J=9.6Hz), 4.75(1H,m), 5.05(1H,m), 4.83 and 5.2(1H,brd), 5.45 and

5.6(1H,dd,J=7.4Hz), 6.2(1H,s), 6.6(1H,m), 6.77(1H,m), 7.0(5H,m)。

(7) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of Boc-Phe(4-F)-OH (63 mg, 0.222 mmol), 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (B) (77 mg, 0.185 mmol) and CMPI (57 mg, 0.222 mmol) in THF (5 ml), TEA (0.08 ml, 0.573 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving the titled compound (0.098 g, 74%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.78(6H,brd), 1.3-1.4(18H,s), 1.8(2H,brd), 2.25(3H,brd), 2.8 and 3.20(7H,brd), 4.1(2H,m), 4.4 and 4.5(1H,d,J=9.89Hz), 4.7 and 5.17(1H,brd), 5.3 and 5.58(1H,d,J=9.89Hz), 6.0 and 6.17(1H,s), 6.6(1H,brd), 6.7-7.2(8H,m)

(8) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A) (279 mg) in methylene chloride (8 ml), TFA (1.3 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (225 mg, 95%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.7 and 0.8(6H,dd,J=6.6 and 6.59Hz), 1.29(9H,s), 2.14 and 2.275(3H,s), 2.1-2.2(1H,m), 2.67 and 2.78(3H,s), 2.6-2.8(2H,m), 3.07(2H,m), 3.7-3.83(1H,m), 4.15 and 4.62(1H,d,J=9.87Hz), 4.98 and 5.18(1H,dd,J=6.5 and 7.6Hz), 6.02 and 6.11(1H,s), 6.55 and 6.8(2H,m), 6.92(1H,d,J=6.92Hz), 6.93-7.15(4H,m)

(9) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B) (93 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1.5 hours and evaporated under reduced pressure to remove the

solvent; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (70 mg, 91.8%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.68, 0.78 and 0.86(6H,dd,J=6.6 and 6.27Hz), 1.3 and 1.32(9H,s), 2.21 and 2.23(3H,s), 2.2-2.4(1H,brd), 2.6 and 2.8(1H,m), 2.71-2.91(3H,s), 3.00(3H,m), 3.77 and 3.9(1H,m), 3.97 and 4.52(1H,d,J=9.37Hz), 4.97 and 5.18(1H,m), 6.12(1H,d,J=3.3Hz), 6.5-7.2(8H,m)

Example 20

5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

(1) Synthesis of Z-Tyr(3-tBu)-H

To a solution of Z-Tyr(3-tBu)-OMe (3.30 g, 8.57 mmol) in THF (200 ml), diisobutyl aluminum hydride (1.0 M toluene solution) (42.9 ml, 42.9 mmol) was added dropwise at -78°C over 15 min. After stirring for 1 hour, the mixture was mixed with methanol and a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.18 g, 72%).

NMR($CDCl_3$):δ 1.37(9H,s), 3.00-3.14(2H,m), 4.40-4.52(1H,m), 4.89(1H,brs), 5.12(2H,s), 5.22-5.32(1H,m), 6.57(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz),7.00(1H,s), 7.30-7.42(5H,m), 9.64(1H,s)

(2) Synthesis of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of Z-Tyr(3-tBu)-H (2.18 g, 6.14 mmol) in ethanol (25 ml), potassium cyanide (480 mg, 7.37 mmol), 30% ammonium carbonate (1.77 g, 18.4 mmol) and water (25 ml) were added and stirred at 60°C for 8 hours. The mixture was left for cooling and mixed with a saturated aqueous $NaHCO_3$ solution. The organic layer was extracted with ethyl acetate and washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.38 g, 53%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 2.90-3.00(2H,m), 3.10-3.22(1H,m), 4.27(1H,brs), 5.06(2H,s), 5.02-5.12(1H,m), 6.07(1H,brs), 6.57(1H,d,J=8.2Hz), 6.88(1H,dd,J=2.0,8.2Hz), 7.10(1H,d,J=2.0Hz), 7.22-7.40(5H,m)

(3) Synthesis of 5-(1-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (543 mg, 1.28 mmol) in methanol (10 ml), 10% palladium

carbon (55 mg) was added and stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; to a solution of the thus obtained residue in THF (13 ml), Z-N-Me-Val-OH (509 mg, 1.92 mmol), CMPI (491 mg, 1.92 mmol) and TEA (0.535 ml, 3.84 mmol) were added under cooling with ice and stirred at room temperature for 3 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving the titled compound (365 mg, 53%).

^{1}H-NMR($CDCl_3$):δ 0.79 and 0.85(6H,d,J=6.6Hz), 2.14-2.26(1H,m), 2.60(3H,s), 2.70-2.92(2H,m), 3.89(1H,d,J=10.8Hz), 4.27(1H,brs), 4.62-4.74(2H,m), 5.14(2H,s), 6.28(1H,d,J=7.9Hz), 6.56-7.10(3H,m), 7.30-7.42(5H,m)

(4) Synthesis of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (363 mg, 0.675 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen

atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (261 mg, 96%).

EI-MS:404(M^+)

^{1}H-NMR(DMSO-d_6):δ 0.79 and 0.82(6H,d,J=6.3-6.6Hz), 1.31(9H,s), 1.90(3H,s), 2.74-2.84(2H,m), 4.02-4.14(1H,m), 4.17(1H,brs), 4.38-4.48(1H,m), 6.64(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz), 6.99(1H,s), 7.85(1H,brs)

(5) Synthesis of 5-(1-(2-(2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (254 mg, 0.629 mmol) in THF (6 ml), Z-Phe(4-F)-OH (239 mg, 0.755 mmol), CMPI (193 mg, 0.755 mmol) and TEA (0.219 ml, 1.57 mmol) were added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (168 mg, 38%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.62,0.71,0.94 and 0.98(6H,d,J=6.0-6.6Hz), 1.34 and 1.37(9H,s), 2.26 and

2.92(3H,s), 2.24-2.42(1H,m), 2.64-3.12(4H,m), 3.84-4.32(2H,m), 4.50-4.82(2H,m), 5.02-5.12(2H,m), 5.20-5.64(1H,m), 6.21(1H,brs), 6.31(1H,brs), 6.50-6.60(2H,m), 6.86-7.14(5H,m), 7.24-7.40(5H,m), 7.50-8.00(1H,m)

(6) Synthesis of 5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (157 mg, 0.223 mmol) in methanol (5 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to preparative TLC (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (83.0 mg, 65%).

FAB-MS:570($M+H^+$)

^{1}H-NMR(DMSO-d_6):(two rotamers)δ 0.48-0.84(6H,m), 1.28, 1.32 and 1.33(9H,s), 2.00-2.12(1H,m), 2.28,2.42 and 2.62(3H,s), 2.40-3.10(4H,m), 3.82-4.08(2H,m), 4.24-4.50(2H,m), 6.58-7.30(7H,m), 7.66-8.30(2H,m), 8.92-9.24(2H,m)

Example 21

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-

hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

(1) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester

To a solution of Z-Tyr(3-tBu)-OMe (4.0 g, 10.39 mmol) in ethanol (100 ml), hydrazine monohydrate (6.4 ml, 103.9 mmol) was added at room temperature. The mixture was stirred overnight and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with ethyl orthoformate (100 ml) and p-toluenesulfonic acid monohydrate (198 mg, 1.04 mmol) at room temperature. The mixture was stirred for 1.5 hours and mixed with 1N HCl (100 ml). The mixture was stirred for 20 min., and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.34 g, 33%).

^{1}H-NMR($CDCl_3$):δ 1.32(9H,s), 3.19(2H,brs), 5.02(1H,brs), 5.05-5.16(2H,m), 5.35(2H,brs), 6.53(1H,d,J=7.9Hz), 6.75(1H,dd,J=7.9,2.0Hz), 6.85(1H,d,J=2.0Hz), 8.34(1H,s)

(2) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine

To a solution of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester (1.25 g, 3.16 mmol) in methanol (30 ml), 10% palladium carbon

(130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.80 g, 97%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 3.02(1H,dd,J=13.8,7.9Hz), 3.18(1H,dd,J=13.8,5.6Hz), 4.47(1H,dd,J=7.9,5.6Hz), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd,J=7.9,2.0Hz), 6.97(1H,d,J=2.0Hz), 8.40(1H,s)

(3) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-N-Me-Val-OH (914 mg, 3.45 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine (0.75 g, 2.87 mmol) and CMPI (881 mg, 3.45 mmol) in THF (30 ml), TEA (0.96 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving 2-benzyloxycarbonylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (1.28 g, 88%).

To a solution of the above compound (1.23 g) in

methanol (24 ml), 10% palladium carbon (120 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.87 g, 96%).

^{1}H-NMR($CDCl_3$):δ 0.70(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.35(9H,s), 1.88-2.03(1H,m), 2.34(3H,s), 2.77(1H,d,J=4.6Hz), 3.12(1H,dd,J=14.0,8.4Hz), 3.28(1H,dd,J=14.0,5.9Hz), 5.45(1H,brs), 5.61-5.71(1H,m), 6.58(1H,d,J=8.0Hz), 6.68(1H,dd,J=8.0,2.0Hz), 6.96(1H,d,J=2.0Hz), 7.84(1H,brd,J=8.9Hz), 8.35(1H,s)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-Phe(4-F)-OH (835 mg, 2.63 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (0.82 g, 2.19 mmol) and CMPI (672 mg, 2.63 mmol) in THF (22 ml), TEA (0.74 ml, 5.26 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column

chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving 2-(2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)amino-N,3-dimethylbutyric acid 1-(1,3,4-oxadiazol-2-yl)-2-(3-t-butyl-4-hydroxyphenyl)ethylamide (1.31 g, 89%).

A mixture of the above compound (1.31 g, 1.95 mmol) and 10% palladium carbon (130 mg) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (752 mg, 72%).

EI-MS:539(M^+)

^{1}H-NMR($CDCl_3$):(two rotamer)δ 0.75, 0.78, 0.89, 0.92(6H,d,J=6.3-6.6Hz), 1.29,1.34(9H,s), 2.24-2.45(1H,m), 2.50-2.85(2H,m), 2.82(3H,s), 3.04-3.20(3H,m), 3.52-3.60,3.72-3.85(1H,m), 3.99,4.43(1H,d,J=10.9Hz), 5.42-5.53,5.64-5.73(1H,m), 6.42-7.18(7H,m), 8.33,8.42(1H,s), 9.62(1H,brd,J=9.2Hz)

Example 22

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

(1) Synthesis of N-Me-Val-Tyr(3-tBu)-NH_2

To a solution of Tyr(3-tBu)-OCH_3 (1.5 g, 5.97 mmol) in MeOH (10 ml), aqueous ammonia (10 ml) was added and

stirred at room temperature overnight. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving Tyr(3-tBu)-NH_2 (1.4 g, 99%).

To a solution of the thus obtained Tyr(3-tBu)-NH_2 (1 g, 4.23 mmol), Z-N-Me-Val-OH (1.23 g, 4.63 mmol) and CMPI (1.2 g, 4.69 mmol) in THF (20 ml), TEA (1.8 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving Z-N-Me-Val-Tyr(3-tBu)-NH_2 (1.7 g, 83%).

A mixture of the thus obtained Z-N-Me-Val-Tyr(3-tBu)-NH_2 (1.7 g), 20% palladium hydroxide/carbon (0.15 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (1.07 g, 88%).

^{1}H-NMR($CDCl_3$):δ 0.67(3H,d,J=6.27Hz), 0.80(3H,d,J=6.6Hz),

1.35(9H,s), 1.91(1H,m), 2.25(3H,s), 2.76(1H,d,J=4.62Hz), 3.00(2H,m), 4.75(1H,q,J=6.6Hz), 6.13(1H,s), 6.55(1H,s), 6.66(1H,d,J=7.92Hz), 6.89(1H,d,J=7.59Hz), 7.02(1H,s), 7.84(1H,d,J=7.91Hz)

(2) Synthesis of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-F)-OH (890 mg, 3.14 mmol), N-Me-Val-Tyr(3-tBu)-NH_2 (1 g, 2.86 mmol) and CMPI (804 mg, 3.15 mmol) in THF (20 ml), TEA (1.2 ml, 7.16 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (1.5 g, 85%).

(3) Synthesis of 2-((2-tertbutoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

A solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (600 mg, 0.976 mmol) and N,N-dimethylacetamide (0.2 ml, 1.5 mmol) in dioxane (3 ml) was stirred at room temperature for 1 hour and mixed with a solution of sodium hydroxide (108 mg) and hydroxyamine hydrochloride (190 mg) in acetic acid/water (7 ml/3 ml). The mixture was stirred at room temperature for 10 min., mixed with water and filtered; a

solution of the thus obtained precipitate in acetic acid/dioxane (10 ml/10 ml) was stirred at 60°C overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (474 mg, 76%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.76, 0.8, 0.86 and 0.98(6H,d,J=6.59,6.93,6.27,and 6.26Hz), 1.28 and 1.32(9H,s), 1.25 and 1.37(9H,s), 2.15(1H,m), 2.35 and 2.92(3H,s), 2.9(3H,m), 3.15(1H,d,J=6.93Hz), 4.12 and 4.49(1H,d,J=6.92Hz), 4.8(1H,m), 5.38 and 5.5(2H,m), 6.65(1H,brd), 6.9-7.2 (7H,m), 8.37(1H,brd)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

To a solution of 2-((2-tertbutoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide (440 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (370

mg, 99%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.75 and 0.87 (total 6H,d and dd,J=6.59 and 6.92Hz), 1.27(9H,s), 2.17(1H,m), 2.77(2H,m), 2.83(3H,s), 3.1(2H,m), 3.55(1H,m), 3.96(1H,d,J=10.89Hz), 5.7(1H,m), 6.45(1H,s), 6.59(1H,d, J=5.94Hz), 6.9(1H.brd), 8.35(1H,s), 9.5(1H,d,J=8.91Hz), 6.95(2H,t,J=8.25Hz), 7.06(2H,t,J=8.25Hz)

Example 23

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide

To a solution of Z-Tyr(3-tBu)-NH_2 (2.08 g, 5.62 mmol) in dioxane (70 ml), Lawesson's reagent (1.36 g, 3.37 mmol) was added and stirred at 80°C for 1 hour. The reaction mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (1.66 g, 77%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 3.01-3.14(2H,m), 4.56-4.65(1H,m), 5.08(2H,s), 6.58(1H,d,J=7.9Hz), 6.90(1H,dd,J=7.9,1.7Hz), 7.09(1H,d,J=1.7Hz), 7.20-7.40(5H,m)

(2) Synthesis of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide (21.49 g, 55.67 mmol) in ethanol (300 ml), bromoacetaldehyde diethylacetal (43 ml, 278 mmol) was added, stirred at 80°C for 2 hours, further mixed with bromoacetaldehyde diethylacetal (43 ml, 278 mmol), stirred at 80°C for 4 hours, further mixed with bromoacetaldehyde diethylacetal (43 ml, 278 mmol) and stirred at 80°C for 3 hours. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (15.32 g, 67%).

^{1}H-NMR($CDCl_3$):δ 1.29(9H,s), 3.10-3.30(2H,m), 5.10(2H,s), 5.20-5.40(1H,m), 6.51(1H,d,J=8.3Hz), 6.74-6.78(2H,m), 7.22 (1H,d,J=3.3Hz), 7.20-7.40(5H,brs), 7.76(1H,d,J=3.3Hz)

(3) Synthesis of 2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine (15.28 g, 37.27 mmol) in methylene chloride (1.1 l), thioanisole (8.75 ml, 74.54 mmol) was added. To the mixture, a solution of 1.0M boron tribromide in methylene chloride (186 ml, 186.34 mmol) was added dropwise under cooling with ice and stirred for 1 hour. The reaction mixture was mixed with water and alkalinized by 2N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced

pressure, giving the titled compound (9.46 g, 90%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 2.82-3.27(2H,m), 4.51-4.56(1H,m), 6.57(1H,d,J=7.9Hz), 6.89(1H,dd,J=7.9,2.0Hz), 6.99(1H,d,J=2.0Hz), 7.27(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(4) Synthesis of 2-(N-tert-butoxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine (4.67 g, 16.64 mmol), Boc-N-Me-Val-OH (5.0 g, 21.63 mmol) and CMPI (5.53 g, 21.63 mmol) in THF (110 ml), TEA (5.33 ml, 38.27 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (8.10 g, 100%).

^{1}H-NMR($CDCl_3$):δ 0.75-0.97(6H,m), 1.29(6H,s), 1.31(3H,s), 1.41(3H,s), 1.48(6H,s), 2.10-2.35(1H,m), 2.71(1.5H,s), 2.73(1.5H,s), 3.10-3.30(2H,m), 3.90-4.10(1H,m), 5.50-5.70(1H,m), 6.58(1H,d,J=7.9Hz), 6.70-6.90(2H,m), 7.20(1H,d,J=3.0Hz), 7.74-7.76(1H,m)

(5) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(N-tert-butoxycarbonyl-N-

methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (8.03 g, 16.42 mmol) in methylene chloride (80 ml), TFA (40 ml) was added and stirred at room temperature for 30 min. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:hexane = 1:2), giving two diastereoisomers A and B of the titled compound, A (2.37 g, 37%) being eluted first and then B (2.17 g, 34%).

(A)

^{1}H-NMR($CDCl_3$):δ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.33(9H,s), 1.85-2.00(1H,m), 2.32(3H,s), 2.75(1H,d,J=4.6Hz), 3.09-3.37(2H,m), 5.63-5.71(1H,m), 6.61(1H,d,J=7.9Hz), 6.87-6.92(2H,m), 7.22(1H,d,J=3.0Hz), 7.77(1H,d,J=3.3Hz)

(B)

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.9Hz), 0.92(3H,d,J=6.9Hz), 1.33(9H,s), 1.95-2.15(1H,m), 2.11(3H,s), 2.68(1H,d,J=5.0Hz), 3.12-3.39(2H,m), 5.60-5.69(1H,m), 6.59(1H,d,J=8.2Hz), 6.87(1H,dd,J=7.9,2.0Hz), 6.93(1H,d,J=2.0Hz), 7.22(1H,d,J=3.3Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(A)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34 mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.55 g, 92%).

^{1}H-NMR($CDCl_3$):δ 0.76(3H,d,J=6.6Hz), 0.86(2H,d,J=6.6Hz), 0.97(1H,d,J=6.6Hz), 1.26(3H,s), 1.29(6H,s), 1.37(6H,s), 1.40(3H,s), 2.15-2.40(1H,m), 2.70-3.50(4H,m), 2.78(3H,s), 4.17(0.3H,d,J=10.2Hz), 4.49(0.7H,d,J=11.2Hz), 4.70-4.85(1H,m), 5.25-5.80(1H,m), 6.58(1H,d,J=7.9Hz), 6.75-7.30(6H,m), 7.21(0.7H,d,J=3.3Hz), 7.23(0.3H,d,J=3.3Hz), 7.74(0.3H,d,J=3.3Hz), 7.77(0.7H,d,J=3.3Hz)

(7) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34

mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.54 g, 92%).

^{1}H-NMR($CDCl_3$):δ 0.57(1H,d,J=6.6Hz), 0.62(1H,d,J=6.9Hz), 0.78(4H,d,J=6.3Hz), 1.33(9H,s), 1.36(9H,s), 2.10-2.30(1H,m), 2.60-3.70(4H,m), 2.82(1.8H,s), 2.85(1.2H,s), 3.99(0.3H,d,J=10.6Hz), 4.51(0.7H,d,J=10.9Hz), 4.70-4.90(1H,m), 5.20-5.60(1H,m), 6.59-7.21(7H,m), 7.20(1H,d,J=3.3Hz), 7.71(1H,d,J=3.3Hz)

(8) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.49 g, 2.28 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (430 mg).

EI-MS:554(M^+)

^{1}H-NMR($CDCl_3$):δ 0.75(2.3H,d,J=6.9Hz), 0.80(0.7H,d,J=6.6Hz), 0.90-0.92(0.7H,m), 0.93(2.3H,d,J=6.6Hz), 1.24(7H,s), 1.30(2H,s), 2.25-2.65(1H,m), 2.70-3.40(4H,m), 2.79(2.4H,s), 2.85(0.6H,s), 3.50-3.60(0.8H,m), 3.75-3.90(0.2H,m), 3.97(0.8H,d,J=10.9Hz), 4.51(0.2H,d,J=10.6Hz), 5.45-5.60(0.2H,m), 5.65-5.80(0.8H,m), 6.55-7.20(7H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(9) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.48 g, 2.26 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography

(developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (587 mg).

EI-MS:554(M^+)

^{1}H-NMR($CDCl_3$):δ 0.72(1.5H,d,J=6.9Hz), 0.786(1.5H,d,J=6.3Hz), 0.793(1.5H,d,J=6.6Hz), 0.88(1.5H,d,J=6.3Hz), 1.24(5.4H,s), 1.33(3.6H,s), 2.15-2.40(1H,m), 2.40-3.35(4H,m), 2.75(1.8H,s), 2.87(1.2H,s), 3.55-3.85(1H,m), 3.86(0.6H,d,J=10.9Hz), 4.56(0.4H,d,J=10.9Hz), 5.50-5.65(1H,m), 6.45-7.15(7H,m), 7.17-7.20(1H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.0Hz)

Example 24

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide

To a solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (400 mg, 0.651 mmol) in methylene chloride (6.5 ml), dimethylformamide dimethylacetal (0.26 ml, 1.954 mmol) was added at room temperature. The mixture was stirred for 30 min. and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue in dioxane (6.5 ml), acetic acid (2 ml) and hydrazine monohydrate (48 μl, 0.977 mmol) were added at room temperature. The mixture was stirred for 40 min., mixed with water and filtered to collect the precipitated solid. The thus obtained solid was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving

2-((2-t-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide (384 mg, 93%).

To a solution of the above compound (421 mg) in methylene chloride (3 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 30 min., mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (175 mg, 49%).

EI-MS:538(M^+)

^{1}H-NMR($CDCl_3$):δ 0.72,0.87,0.73-0.80(6H,d,J=6.3-6.6Hz), 1.22, 1.25(9H,s), 2.24-2.41(1H,m), 2.50-3.30(4H,m), 2.78, 2.87(3H,s), 3.47-3.58, 3.79-3.88(1H,m), 4.00,4.39(1H,brd,J=10.6Hz), 5.29-5.38,5.40-5.50(1H,m), 6.41-7.11(7H,m), 7.52,9.33(1H,brd,J=8.3Hz), 8.02,8.10(1H,s)

Example 25

2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of 2-tert-butoxycarbonylamino-3-

methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of Boc-Val-OH (890 mg, 4.09 mmol), 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.03 g, 3.73 mmol) and CMPI (653 mg, 1.05 mmol) in THF (10 ml), TEA (1 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.88 g, 99%).

^{1}H-NMR($CDCl_3$):δ 0.79 and 0.89(6H,d,J=6.93Hz), 1.29 and 1.31(9H,s), 1.42 and 1.44(9H,s), 2.15(1H,brd), 3.23(2H,m), 3.89(1H,m), 5.0(1H,brd), 5.4(0.7H, brd), 5.57(1H,q,J=6.93 and 5.92Hz), 6.56(1H,q,J=4.62 and 4.29Hz), 6.8(3H,brd), 7.21(1H,m), 7.75(1H,t,J=2.07 and 3.3Hz)

(2) Synthesis of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.7 g) in methylene chloride (14 ml), TFA (6 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene

chloride:methanol:ethyl acetate = 20:1:2), giving two diastereoisomers A and B of the titled compound, A (700 mg) being eluted first and then B (650 mg, 99%).

(A)

^{1}H-NMR($CDCl_3$-CD_3OD):δ 0.89(6H,brd), 1.28(9H,s), 2.15(1H,m), 3.18-3.7(3H,m), 5.48(1H,brd), 6.6(1H,brd), 6.8(2H,brd), 7.27(1H,s), 7.7(1H,s)

(B)

^{1}H-NMR($CDCl_3$-CD_3OD):δ 0.72(6H,d,J=6.27Hz), 1.31(9H,s), 1.92(1H,brd), 3.04(2H,brd), 3.28(1H,dd,J=5.28 and 5.6Hz), 5.55(1H,m), 6.62(1H,d,J=7.92Hz), 6.86(1H,brd), 6.97(1H,s), 7.28(1H,s), 7.68(1H,d,J=2.64Hz)

(3) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (600 mg, 1.59 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml), $NaBH_3CN$ (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled

compound (935 mg, 93%).

^{1}H-NMR($CDCl_3$):δ 0.75 and 0.83(6H,d,J=6.93 and 6.59Hz), 1.36(9H,s), 1.42(9H,s), 2.46(2H,brd), 2.66(2H,brd), 2.73(1H,d, J=4.61Hz), 2.81(1H,d, J=7.26Hz), 3.20(2H,d,J=6.26Hz), 3.6(2H,m), 3.8(1H,brd), 4.7(1H,brd), 5.6(1H,q,J=6.93 and 5.94Hz), 6.61(1H,d,J=7.92Hz), 6.77(1H,s), 6.85(1H,d,J=7.92Hz), 6.9-7.21(8H,m), 7.66(1H,d,J=2.97Hz)

(4) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (600 mg, 1.59 mmol) and 1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml), $NaBH_3CN$ (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (950 mg, 95%).

^{1}H-NMR($CDCl_3$):δ 0.83 and 0.87(6H,d,J=6.93 and 6.92Hz), 1.34(9H,s), 1.41(9H,s), 2.00(1H,brd), 2.31(2H,brd), 2.6-2.81(3H,brd), 2.81(1H,d, J=7.26Hz), 3.20(2H,m), 3.6(2H,m),

3.8(1H,brd), 4.58(1H,brd), 4.83(1H,brd), 5.59(2H,q,J=6.93Hz), 6.60(1H,d,J=7.92Hz), 6.81(1H,d,J=7.91Hz), 6.88(1H,s), 6.9-7.21(8H,m), 7.74(1H,d,J=2.29Hz)

(5) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (300 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (180 mg, 71%).

^{1}H-NMR(DMSO-d_6):δ 0.78 and 0.88(6H,d,J=3.3 and 5.6Hz), 1.28(9H,s), 1.90(1H,brd), 2.6(1H,m), 2.7-3.0(3H,brd), 3.1(2H,m), 3.4(1H,brd), 5.29(1H,q,J=5.93 and 8.58Hz), 6.69(1H,d,J=7.92Hz), 6.86(1H,d,J=7.59Hz), 6.95(1H,s), 7.2(4H,m), 7.62(1H,d,J=2.97Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (300

mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (193 mg, 76%).

^{1}H-NMR(DMSO-d_6):δ 0.61(6H,q,J=6.6 and 12.54Hz), 1.3(9H,s), 1.72(1H,s), 2.7-3.0(4H,brd), 3.16(1H,s), 3.28(1H,m), 3.5(1H,brd), 5.37(1H,m), 6.65(1H,d,J=8.25Hz), 6.85(1H,d,J=10.89Hz), 7.0(1H,s), 7.2(4H,m), 7.68(1H,d,J=2.97Hz), 7.81(1H,d,J=3.3Hz)

Example 26

Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Tyr(2-F)-OH (0.60 g, 3.01 mmol) and di-tert-butyl dicarbonate (0.69 g, 3.16 mmol) in dioxane/water (5 ml/5 ml), TEA (0.84 ml, 6.02 mmol) was added under cooling with ice and stirred for 2 hours. The reaction mixture was concentrated to approximately a half volume, mixed with a saturated aqueous $NaHCO_3$ solution and washed with ether. The aqueous layer was rendered acidic by the addition of 2N hydrochloric acid under cooling with ice, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Boc-Tyr(2-F)-OH (0.85 g).

To a solution of the above crude Boc-Tyr(2-F)-OH (0.82 g), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.77 g, 2.11 mmol) and CMPI (0.81 g, 3.17 mmol) in THF (5 ml), TEA (1.18 ml, 8.44 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.21 g, 15%).

(2) Synthesis of Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.326 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous $NaHCO_3$ solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (173 mg, 82%).

EI-MS(M^+):544

^{1}H-NMR(DMSO-d_6-$CDCl_3$):δ 0.21(6/5H,d,J=6.3Hz), 0.59(6/5H,d,J=6.6Hz), 0.71(9/5H,d,J=6.6Hz), 0.84-0.98(9/5H,m), 1.30(27/5H,s), 1.37(18/5H,s), 2.00-2.22(1H,m), 2.10(6/5H,s), 2.3-2.8(2H,m), 2.44(9/5H,s),

2.85(9/5H,d,J=5.9Hz), 3.1-3.8(2H,m), 3.24(6/5H,d,J=5.0Hz), 3.94-4.20(1H,m), 4.51(2/5H,d,J=10.2Hz), 4.78(2/5H,dd,J=3.9,11.2Hz), 4.88(3/5H,d,J=10.2Hz), 5.41(3/5H,dd,J=3.9,10.2Hz), 6.48-7.21(7.7H,m), 7.60-7.75(0.3H,m), 8.88(1H,d,J=7.3Hz), 9.47(1H,brs)

Example 27

$Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2$

(1) Synthesis of $Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2$

To a solution of Tyr(3-F)-OH (0.80 g, 4.02 mmol) and di-tert-butyl dicarbonate (0.92 g, 4.22 mmol) in dioxane/water (7 ml/7 ml), TEA (1.12 ml, 8.04 mmol) was added under cooling with ice and stirred for 2.5 hours. The reaction mixture was concentrated to approximately a half volume, mixed with a saturated aqueous $NaHCO_3$ solution and washed with ether. The aqueous layer was rendered acidic by the addition of 2N hydrochloric acid under cooling with ice, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Boc-Tyr(3-F)-OH (1.18 g).

To a solution of the above crude Boc-Tyr(3-F)-OH (1.18 g), $N-Me-Val-N-Me-Tyr(3-tBu)-NH_2$ (1.10 g, 3.03 mmol) and CMPI (1.16 g, 4.55 mmol) in THF (6 ml), TEA (1.27 ml, 12.1 mmol) was added under cooling with ice and stirred at room temperature for 27 hours. The reaction mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.19 g, 10%).

(2) Synthesis of Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.19 g, 0.294 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous $NaHCO_3$ solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (136 mg, 85%).

EI-MS(M^+):544

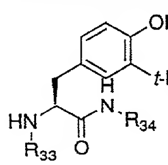
^{1}H-NMR (DMSO-d_6-$CDCl_3$):δ 0.18(6/5H,d,J=6.3Hz), 0.58(6/5H,d,J=6.6Hz), 0.68(9/5H,d,J=6.6Hz), 0.85(9/5H,d,J=6.3Hz), 1.29(27/5H,s), 1.37(18/5H,s), 1.95-2.21(1H,m), 2.04(6/5H,s), 2.30-3.00(2H,m), 2.41(9/5H,s), 2.81(9/5H,s), 3.10-3.60(16/5H,m), 3.55-6.64(3/5H,m), 4.00-4.10(2/5H,m), 4.45(2/5H,d,J=10.2Hz), 4.70(2/5H,dd,J=3.9,11.2Hz), 4.85(3/5H,d,J=10.2Hz), 5.38(3/5H,dd,J=3.9,10.2Hz), 6.51-7.31(8H,m), 8.98(1H,d,J=2.6Hz), 9.50(1H,brs)

Examples 28-64 were conducted according to Scheme 1

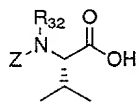
and Examples 65-78 were conducted according to Scheme 2. The following Reference Examples show the methods of preparing Intermediates of Schemes 1 and 2. Table C-1 shows structural formulae of Intermediates of Examples 28-64.

Table C-1

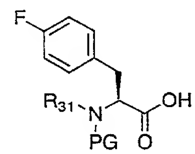
Intermediates of Examples 28-78



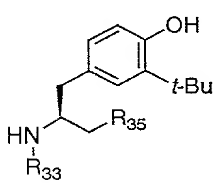
T 1 : R33=R34=H
T 2 : R33=H, R34=Me
T 4 : R33=Me, R34=H (Example 1(5))
T 5 : R33=R34=Me
T 7 : R33=Et, R34=H
T 8 : R33=Et, R34=Me
T 1 7 : R33=Me, R34=$CH_2SO_2CH_3$
T 1 8 : R33=H, R34=tBu



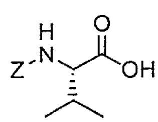
V1:R32=Me (Commercial)
V2:R32=Et



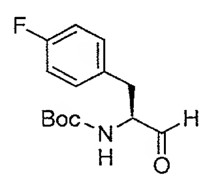
P1:PG=Boc, R31=H (Commercial)
P2:PG=Boc, R31=Me
P3:PG=Z, R31=Et
P10:PG=Boc, R31=Et



T19:R33=H, R35=OH (Example 17)
T20:R33=Me, R35=H
T21:R33=R35=H
T22:R33=H, R35=NHBoc (Example 10)
T23:R33=Me, R35=OH



V4 (Commercial)



P 1 1

In Table C-1, "(Example 1 (5))", "(Example 17)" and "(Example 10)" mean that the methods of preparing the compounds are described in the corresponding Examples 1 (5), 17 and 10, respectively. "Commercial" means that the compound is commercially available.

Reference Example 1

Synthesis of Intermediate T1

A mixture of Tyr(3-tBu)-OMe (12.4 g, 49 mmol) and concentrated aqueous ammonia (240 ml) was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography ($CHCl_3$:MeOH = 10:1), giving Tyr(3-tBu)-NH_2 (T1) (10 g, 80%).
^{1}H-NMR($CDCl_3$):δ 1.40(9H,s), 2.63(1H,dd,J=9.6,13.9Hz), 3.19(1H,dd,J=4.0,13.9Hz), 3.58(1H,dd,J=4.0,9.6Hz), 5.11(1H,brs), 5.38(1H,brs), 6.64(1H,d,J=7.9Hz), 6.92(1H,dd,J=2.0,7.9Hz), 7.11(1H,d,J=2.0Hz).

Reference Example 2

Synthesis of Intermediate T2

A mixture of Tyr(3-tBu)-OMe (12 g, 48 mmol) and a 40% methylamine methanol solution (80 ml) was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure, giving Tyr(3-tBu)-NHMe (T2) (12 g) as a crude product.
^{1}H-NMR($CDCl_3$):δ 1.39(9H,s), 2.60(1H,dd,J=9.6,13.9Hz), 2.83(3H,d,J=5.0Hz), 3.18(1H,dd,J=4.0,13.9Hz), 3.57(1H,dd,J=4.0,9.6Hz), 6.67(1H,d,J=7.9Hz), 6.88(1H,dd,J=1.8,7.9Hz), 7.07(1H,d,J=1.8Hz).

Reference Example 3

Synthesis of Intermediate T5

(1) Synthesis of N-formyl-Tyr(3-tBu)-OMe

To a solution of acetyl chloride (22.6 ml, 299 mmol) in diethyl ether (1 l), sodium formate (30.6 g, 450 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was filtered and evaporated to remove the solvent. The thus obtained residue was added dropwise to a solution of H-Tyr(3-tBu)-OMe (22.2 g, 83.8 mmol) in methylene chloride (500 ml) under cooling with ice, mixed with TEA (46.7 ml, 335 mmol) and stirred at room temperature for 2 hours. The reaction mixture was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving N-formyl-Tyr(3-tBu)-OMe (23.8 g, 100%).

^{1}H-NMR ($CDCl_3$):δ 1.38(9H,s), 3.09(2H,d,J=5.3Hz), 3.76(3H,s), 4.93(1H,dd,J=5.3,13.5Hz), 5.23(1H,s), 6.02(1H,d,J=13.5Hz), 6.55(1H,d,J=7.9Hz), 6.80(1H,dd,J=2.0,7.9Hz), 6.95(1H,d,J=2.0Hz), 8.18(1H,s).

(2) Synthesis of N-Me-Tyr(3-tBu)-OMe

To a solution of N-formyl-Tyr(3-tBu)-OMe (23.8 g, 85.3 mmol) in THF (400 ml), 1.0M borane-THF complex (170 ml) was added dropwise under cooling with ice over 30 min. The mixture was stirred for 20 min., mixed with methanol (50 ml) and further stirred for 30 min. The reaction mixture was mixed with 33% hydrobromic acid/acetic acid (31

ml) and stirred for 2 hours. The mixture was neutralized by saturated aqueous $NaHCO_3$ under cooling with ice and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me-Tyr(3-tBu)-OMe (20.3 g, 90%).

^{1}H-NMR ($CDCl_3$):δ 1.38(9H,s), 2.37(3H,s), 2.89(2H,d,J=6.6Hz), 3.42(1H,t,J=6.6Hz),3.68(3H,s), 6.55(1H,d,J=7.9Hz), 6.86(1H,dd,J=2.0,7.9Hz), 7.02(1H,d,J=2.0Hz)

(3) Synthesis of N-Me-Tyr(3-tBu)-NHMe

To a solution of N-Me-Tyr(3-tBu)-OMe (8.20 g, 31.1 mmol) in methanol (20 ml), a 30% methylamine methanol solution (200 ml) was added and stirred at room temperature for 16 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me- Tyr(3-tBu)-NHMe (T5) (6.27 g, 76%).

^{1}H-NMR ($CDCl_3$):δ 1.39(9H,s), 2.26(3H,s), 2.58(1H,dd,J=10.5,14.8Hz), 2.84(2H,d,J=4.9Hz), 3.06-3.18(2H,m), 5.00(1H,brs), 6.62(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 7.08(1H,d,J=1.7Hz), 7.15(1H,brs).

Reference Example 4

Synthesis of Intermediate T7

A mixture of Tyr(3-tBu)-NH_2 (1.6 g, 6.8 mmol) and acetaldehyde (7.6 ml, 0.14mol) was stirred under cooling with ice for 10 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (34 ml) and then under cooling with ice with sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography ($CHCl_3$:MeOH = 20:1), giving N-Et-Tyr(3-tBu)-NH_2 (T7) (1.3 g, 73%).

^{1}H-NMR($CDCl_3$):δ 0.96(3H,t,J=7.3Hz), 1.40(9H,s), 2.4-2.7(3H,m), 3.14(1H,dd,J=4.0,13.9Hz), 3.26(1H,dd,J=4.0,9.6Hz), 5.25(1H,s), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.10(1H,d,J=2.0Hz), 7.18(1H,brs).

Reference Example 5

Synthesis of Intermediate T8

A mixture of Tyr(3-tBu)-NHMe (1.7 g, 6.8 mmol), acetaldehyde (0.76 ml, 13.6 mmol) and dichloromethane (10 ml) was stirred under cooling with ice for 30 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (20 ml) and then under cooling with ice with

sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated under reduced pressure under cooling with ice; the thus obtained residue was subjected to silica gel column chromatography ($CHCl_3$:MeOH=20:1), giving N-Et- Tyr(3-tBu)-NHMe (T8) (1.7 g, 90%).

^{1}H-NMR($CDCl_3$):δ 0.94(3H,t,J=7.3Hz), 1.39(9H,s), 2.4-2.6(2H,m), 2.60(1H,dd,J=9.6,13.8Hz), 2.83(3H,d,J=4.9Hz), 3.13(1H,dd,J=4.0,13.8Hz), 3.25(1H,dd,J=4.0,9.6Hz), 5.44(1H,brs),6.64(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.07(1H,d,J=2.0Hz), 7.27(1H,brs)

Reference Example 6

Synthesis of Intermediate V2

To a solution of Z-Val-OH (50 g) in THF (500 ml), ethyl iodide (127.3 ml, 1592 mmol) was added under cooling with ice and then sodium hydride (60% in oil) (23.88 g, 597 mmol) was added slowly, followed by stirring at 60°C for 12 hours. The reaction mixture was mixed with water and washed with ether. The thus obtained aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The resultant was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (H:EA:AcOH = 100:50:1),

giving Z-N-Et-Val-OH (V2) (29.29 g, 53%).

^{1}NMR($CDCl_3$):δ 0.92(3H,d,J=6.3Hz), 1.03(3H,d,J=6.6Hz), 1.16(3H,t,J=6.9Hz), 2.40-2.60(1H,m), 3.15-3.58(2H,m), 3.73(1H,brd,J=10.9Hz), 5.20(2H,brs), 7.36(5H,brs)

Reference Example 7

Synthesis of Intermediate P2

To a solution of Boc-Phe(4-F)-OH (13.4 g, 47.3 mmol) in THF (100 ml), 60% sodium hydride (5.7 g, 142 mmol) and then methyl iodide (23.6 ml, 378 mmol) were added under cooling with ice. The mixture was stirred at room temperature for 38 hours, under cooling with ice, mixed with water and washed with n-hexane. Under cooling with ice, the aqueous layer was rendered acidic by 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with ether and n-hexane and the thus formed precipitate was collected by filtration to give Boc-N-Me-Phe(4-F)-OH (P2) (11.4 g, 81%).

^{1}H-NMR($CDCl_3$):δ 1.32 and 1.39(9H,s), 2.67 and 2.75(3H,s), 2.94-3.11(1H,m), 3.20-3.35(1H,m), 4.53-4.62(1H,brd), 4.97(1H,brs), 6.90-7.20(4H,m)

Reference Example 8

Synthesis of Intermediate P3

To a solution of Z-Phe(4-F)-OH (13.9 g, 44.0 mmol) in

THF/DMF (73 ml/37 ml), ethyl iodide (28.1 ml, 352 mmol) and 60% sodium hydride (5.28 g, 132 mmol) were added under cooling with ice and stirred at room temperature for 5.5 hours. Water was added slowly to the reaction mixture, followed by washing with ether. The aqueous layer was adjusted to pH 3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:acetic acid = 100:50:1), giving Z-N-Et-Phe(4-F)-OH (P3) (10.9 g, 72%).

Reference Example 9

Synthesis of Intermediate P10

To a solution of Boc-Phe(4-F)-OH (1.0 g, 3.53 mmol) in THF/DMF (6 ml/1.5 ml), ethyl iodide (2.24 ml, 20.8 mmol) and 60% sodium hydride (422 mg, 10.6 mmol) were added under cooling with ice and stirred at room temperature for 19 hours. The reaction mixture was mixed with water slowly and then with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:15), giving Boc-N-Et-Phe(4-F)-OH (P10) (593 mg, 54%).

Reference Example 10

Synthesis of Intermediate T17

A suspension of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (2.5 g, 5.27 mmol), a 35% aqueous formaldehyde solution (10 ml) and potassium carbonate (2.19 g, 15.8 mmol) in acetonitrile was stirred for 2 hours. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous NH_4Cl solution and then with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:1), giving Z-N-Me-Phe(3-tBu-4-benzyloxy)-$NHCH_2OH$ (2.0 g).

To a solution of the above compound (2.0 g, 3.97 mmol) in 85% formic acid (30 ml), sodium methanesulfinate (1.5 g, 15.3 mmol) was added and then stirred at 50°C for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; to a solution of the thus obtained residue (1.8 g) in methanol (20 ml), 20% palladium hydroxide/carbon (0.50g) was added and stirred in a hydrogen atmosphere for 2 days. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:methanol:methylene chloride

=1:1:15), giving N-Me-Phe(3-tBu-4-benzyloxy)-$NHCH_2SO_2CH_3$ (T17) (890 mg).

Reference Example 11

Synthesis of Intermediate T18

To a solution of Z-Tyr(3-tBu)-OMe (1.01 g, 2.62 mmol) in methanol/water (12 ml/3 ml), lithium hydroxide monohydrate (0.17 g, 3.93 mmol) was added and stirred at room temperature for 2 hours. The reaction mixture was washed with ether, rendered acidic by 2N hydrochloric acid and extracted with methylene chloride. The extract was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-Tyr(3-tBu)-OH (0.98 g).

To a solution of the above crude compound (0.92 g, 2.48 mmol), WSCI (0.52 g, 2.73 mmol) and HOBT (0.37 g, 2.73 mmol) in DMF (15 ml), tert-butylamine (0.31 ml, 2.48 mmol) and then NMM (0.29 ml, 2.73 mmol) were added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, a saturated aqueous $NaHCO_3$ solution and saturated brine in that order. The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving Z-Tyr(3-tBu)-NHtBu (1.05 g, 99%).

To a solution of the above compound (1.0 g, 2.34

mmol) in methanol (20 ml), 20% palladium hydroxide/carbon (0.16 g) was added and stirred in a hydrogen atmosphere for 2 hours. The reaction mixture was filtered with Celite and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude Tyr(3-tBu)-NHtBu (T18) (0.60 g, 88%).

Reference Example 12

Synthesis of Intermediate T20

(1) Synthesis of 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (27.8 g, 58.5 mmol) in THF (290 ml), ethyl chloroformate (6.2 ml, 64.3 mmol) and N-methyl morpholine 7.7 ml, 70.2 mmol) were added under cooling with ice and stirred. After 2 hours, the reaction mixture was mixed with sodium borohydride (6.7 g, 175 mmol), water (100 ml) and methanol (100 ml) and stirred at room temperature for 6 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:1:2), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-1-hydroxymethyl-N-methylethylamine (12.4 g, 46%).

A solution of the above compound (5.21 g, 11.2 mmol) in methylene chloride (55 ml), TEA (2.34 ml, 16.8 mmol) and methanesulfonyl chloride (0.954 ml, 12.3 mmol) were added under cooling with ice and stirred for 30 min. Under cooling with ice, the reaction mixture was mixed with saturated aqueous $NaHCO_3$ and extracted with methylene chloride. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving a mesylate. To a solution of the mesylate in THF (30 ml), a 1M lithium triethyl borohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 1 hour, further lithium triethylborohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 30 min., the mixture was mixed with water under cooling with ice and extracted with chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine (3.42 g, 68%).

^{1}H-NMR($CDCl_3$):δ 1.14(3H,d,J=6.9Hz), 1.36(9H,s), 2.50-2.80(2H,m), 2.76 and 2.83(total 3H,s), 4.30-4.58(1H,m), 4.88-5.10(4H,m), 6.74-7.14(3H,m), 7.20-7.50(10H,m)

(2) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-N-methyl-1-methylethylamine (T20)

A suspension of 2-(4-benzyloxy-3-tert-butylphenyl)-N-

benzyloxycarbonyl-N-methyl-1-methylethylamine (3.30 g, 7.35 mmol) and 20% palladium hydroxide/carbon catalyst (350 mg) in methanol (100 ml) was stirred in a hydrogen atmosphere for 1.5 hours. The mixture was filtered to remove the catalyst and the filtrate was evaporated to remove the solvent under reduced pressure, giving 2-(3-tert-butyl-4-hydroxyphenyl)-N-methyl-1-methylethylamine (T20) (1.62 g, 100%).

^{1}H-NMR($CDCl_3$):δ 1.12(3H,d,J=6.3Hz), 1.38(9H,s), 2.42(3H,s), 2.64(2H,d,J=6.6Hz), 2.75-2.90(1H,m), 6.55(1H,d,J=7.9Hz), 6.84(1H,dd,J=1.6,7.9Hz), 7.04(1H,d,J=1.6Hz).

Reference Example 13

Synthesis of Intermediate T21

(1) Synthesis of Z-N,O-dibenzyl-Tyr(3-tBu)-OMe

To a solution of Z-Tyr(3-tBu)-OMe (3.0 g, 7.78 mmol) in DMF (20 ml), under cooling with ice, sodium hydride (0.68 g, 17.1 mmol) was added and stirred for 15 min., followed by the addition of benzylbromide (2.3 ml, 19.5 mmol). The reaction mixture was stirred for 3 hours, mixed with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving the titled compound (4.14 g, 94%).

(2) Synthesis of N-benzyl-2-(4-benzyloxy-3-tert-

butylphenyl)-1-methyl-N-(benzyloxycarbonyl)ethylamine

To a solution of Z-N,O-dibenzyl-Tyr(3-tBu)-OMe (4.14 g, 7.32 mmol) in ethanol/THF (36 ml/6 ml), a 2M lithium borohydride/THF solution (11.0 ml, 22.0 mmol) was added under cooling with ice and stirred at room temperature overnight. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium and evaporated to remove the solvent under reduced pressure. The thus obtained residue was dissolved in methylene chloride (50 ml) and under cooling with ice mixed with triethylamine (2.0 ml, 14.4 ml) and then with methanesulfonyl chloride (0.72 ml, 9.36 mmol), followed by stirring for 30 min. The reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was dissolved in THF (10 ml) and mixed with a 1M lithium triethyl borohydride/THF solution (28.0 ml, 28.0 mmol). The mixture was stirred for 3 hours, mixed with water under cooling with ice and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving the titled compound (2.35 g, 61%).

(3) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-1-

methylethylamine

A suspension of N-benzyl-2-(4-benzyloxy-3-tert-butylphenyl)-1-methyl-N-(benzyloxycarbonyl)-ethylamine (2.35 g, 4.50 mmol) and 20% palladium hydroxide/carbon catalyst (0.50 g) in methanol (30 ml) was stirred in a hydrogen atmosphere overnight. The mixture was filtered to remove the catalyst and the filtrate was evaporated to remove the solvent under reduced pressure, giving 2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethylamine (T21) (0.90 g, 96%).

^{1}H-NMR($CDCl_3$):δ 1.16(3H,d,J=6.6Hz), 1.39(9H,s), 2.45(1H,dd,J=4.9, 13.3Hz), 2.69(1H,dd,J=4.9,13.3Hz), 3.15(1H,m), 3.52H,brs), 6.58(1H,d,J=7.9Hz), 6.83(1H,dd,J=1.6,7.9Hz), 7.03(1H,d,J=1.6Hz).

Reference Example 14

Synthesis of Intermediate T23

To a solution of Tyr(3-tBu)-OMe (3.0 g, 11.9 mmol) in 1,4-dioxane/water (12 ml/12 ml), sodium carbonate (1.9 g, 17.9 mmol) and then ethyl chlorocarbonate (1.26 ml, 13.1 mmol) were added under cooling with ice and stirred for 2 hours. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue (3.85 g) in THF (120 ml), lithium aluminum hydride (2.83 g, 59.7 mmol) was added little by little and stirred at 60°C for 5 hours. The reaction mixture was poured into ice water,

stirred and then filtered with Celite for removing insoluble material. The filtrate was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (methylene chloride:methanol = 3:1), giving 3-(3-tert-butyl-4-hydroxyphenyl)-2-methylaminopropanol (T23) (1.9 g, 67%, in 2 steps).

Reference Example 15

Synthesis of Intermediate P11

(1) Synthesis of 2-(4-fluorophenyl)-1-(N-methoxy-N-methylcarbamoyl)ethylcarbamic acid tert-butyl ester

To a solution of Boc-Phe(4-F)-OH (5.0 g, 17.7 mmol) in methylene chloride (89 ml), BOP reagent (9.39 g, 21.2 mmol), N,O-dimethylhydroxylamine hydrochloride (2.07 g, 21.2 mmol) and TEA (5.92 ml, 42.5 mmol) were added under cooling with ice and stirred for 30 min. The reaction mixture was mixed with water and extracted with methylene chloride. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (5.76 g, 100%).

^{1}H-NMR ($CDCl_3$): δ 1.39(9H,s), 2.84(1H,dd,J=6.9,13.8Hz), 3.02(1H,dd,J=5.9,13.8Hz), 3.16(3H,s), 3.68(3H,s), 4.86-4.96(1H,m), 5.10-5.24(1H,m), 6.95(1H,d,J=8.9Hz),

6.98(1H,d,J=8.9Hz), 7.11(1H,d,J=8.2Hz), 7.13(1H,d,J=8.2Hz).

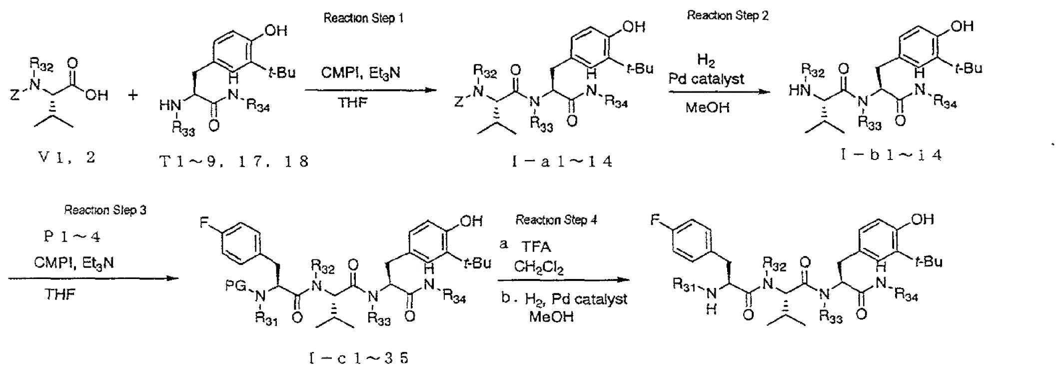
(2) Synthesis of 2-(4-fluorophenyl)-1-formylethylcarbamic acid tert-butyl ester (P11)

To a solution of the above compound (3.30 g, 10.1 mmol) in diethyl ether (150 ml), lithium aluminum hydride (498 mg, 13.1 mmol) was added under cooling with ice and stirred for 30 min. The reaction mixture was mixed with a solution of potassium hydrogen sulfate (2.75 g, 20.2 mmol) in water (20 ml) and stirred for 1 hour. The reaction mixture was filtered and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving the titled compound (2.37 g, 88%).

^{1}H-NMR($CDCl_3$): δ 1.44(9H,s), 3.00-3.20(2H,m), 4.34-4.46(1H,m), 4.98-5.06(1H,m), 6.98(1H,d,J=8.6Hz), 7.01(1H,d,J=8.6Hz), 7.12(1H,d,J=8.3Hz), 7.14(1H,d,J=8.3Hz), 9.63(1H,s).

Scheme 1 shows the synthesis scheme of Examples 28-64.

Scheme 1: synthesis scheme of Examples 28-64



Synthesis process shown in scheme 1 is explained below:

Reaction step 1

To a solution of Compounds T and V and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a.

Reaction step 2

To a solution of Compound I-a in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b.

Reaction step 3

To a solution of Compounds I-b and P and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c.

Reaction step 4a (PG=Boc)

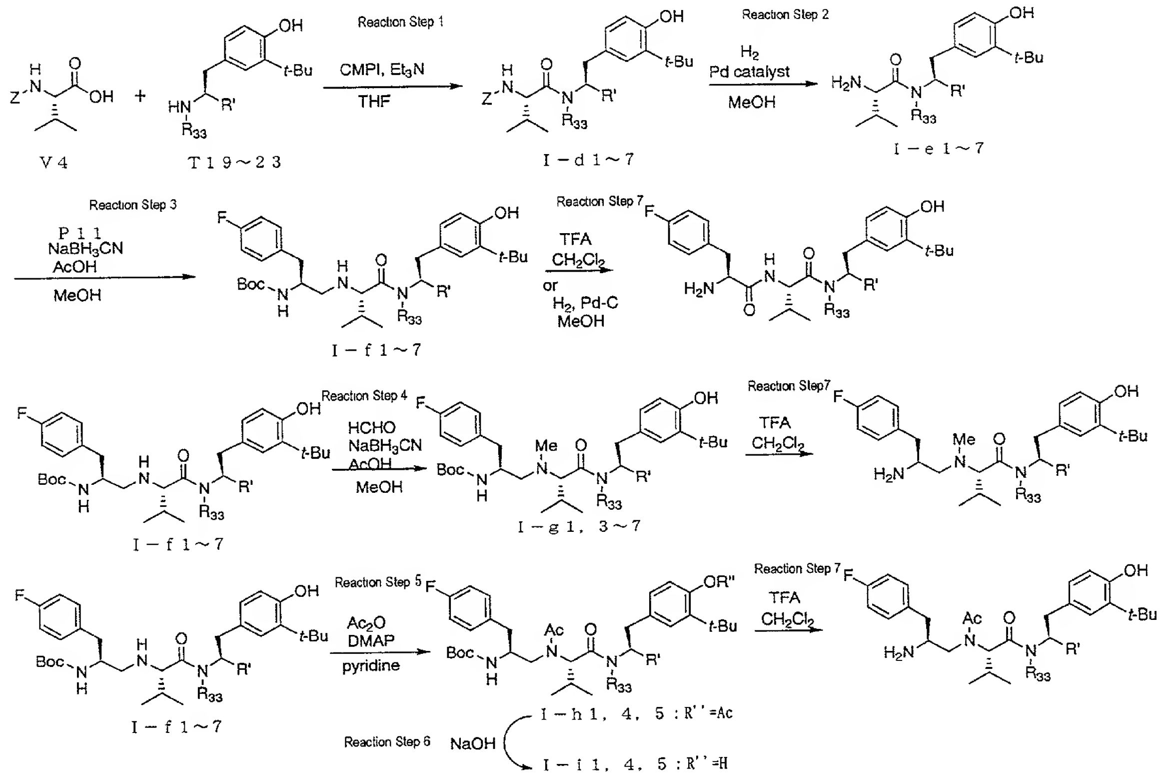
To a solution of Compound I-c in methylene chloride, TFA was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Reaction step 4b (PG=Z)

To a solution of Compound I-c in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Scheme 2 shows the synthesis scheme of Examples 65-78.

Scheme 2: synthesis scheme of Examples 65-78



Synthesis process shown in scheme 2 is explained below:

Reaction step 1

To a solution of Compounds T and V4 and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium

sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-d.

Reaction step 2

To a solution of Compound I-d in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium catalyst and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-e.

Reaction step 3

To a solution of Compounds P11 and I-e in methanol, acetic acid and sodium cyanoborohydride were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-f.

Reaction step 4

To a solution of Compound I-f in methanol, 35% aqueous formaldehyde solution, acetic acid and sodium cyanoborohydride were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was washed with saturated

brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-g.

Reaction step 5

To a solution of Compound I-f in pyridine, acetic acid anhydride and 4-dimethylaminopyridine were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous copper sulfate solution, water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-h.

Reaction step 6

To a solution of Compound I-h in methanol, a 2N aqueous sodium hydroxide solution was added and stirred at room temperature. The reaction mixture was mixed with saturated aqueous NH_4Cl and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-i.

Reaction step 7

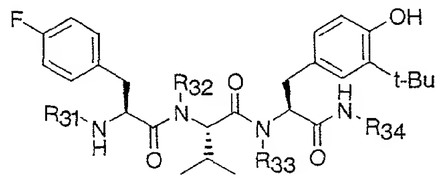
To a solution of Compound I-f, or I-g, or I-i in methylene chloride, TFA was added and stirred at room

temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Examples conducted according to Scheme 1 are shown in Tables D-1 to D-43.

Table D-1

Structural Formula of Compounds of Example 28-64



Example 28

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	H	H

Reaction 1

Compound T1:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.35	1.3	2.1	40	19	EA:H 3:1	I-a1	1.6

^{1}H-NMR($CDCl_3$):δ 0.84 and 0.88(6H,d,J=6.6Hz), 1.36(9H,s), 2.15-2.35(1H,m), 2.75(3H,s), 2.8-3.1(2H,m), 4.02(1H,brd,J=11.2Hz), 4.5-4.7(1H,m), 5.13 and 5.15(2H,s), 5.3-5.5, 5.5-5.7, 5.8-6.0, 6.1-6.2, and 6.5-6.8(3H,m), 6.45(1H,d,J=7.9Hz), 6.81(1H,brd,J=7.9Hz), 7.07(1H,brs), 7.37(5H,s)

Reaction 2

Compound I-a1:g	$Pd(OH)_2$ g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
1.5	0.3	30	1	Not purified	I-b1	1.1

^{1}H-NMR($CDCl_3$):δ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.37(9H,s), 1.8-2.0(1H,m), 2.30(3H,s), 2.74(1H,d,J=4.3Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.3-5.7(1H,m), 6.1-6.3(1H,m), 6.5-6.7(1H,m), 6.93(1H,brd,J=7.9Hz), 7.06(1H,brs), 7.6-7.8(1H,m)

Table D-2

Example 28(Continued from Table D-1)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2

Reaction 3								
Compound I-b1:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.3	0.29	0.26	0.43	5	18	MC:M 20:1	I-c1	0.45
^{1}H-NMR($CDCl_3$):δ 0.77, 0.89, and 1.01(6H,d,J=6.6Hz), 1.33, 1.36, 1.37, and 1.39(18H,s), 2.15-2.4(1H,m), 2.32 and 2.77(3H,s), 2.7-3.0(4H,m), 4.1-4.3, 4.5-4.6, and 4.6-4.8(2H,m), 5.36(1H,brd,J=8.9Hz), 5.44, 5.57, 5.71, 5.75, and 6.18(3H,brs), 6.6-7.2(7H,m), 7.8-7.9(1H,m)								

Reaction 4a						
Compound I-c1:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.4	2	4	0.5	CH:M:N 400:10:1	0.32	17.8
EI-MS(M^+):514 ^{1}H-NMR($CDCl_3$):δ 0.71, 0.79, 0.91, and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.38(9H,s), 2.2-2.4(1H,m), 2.4-3.2(4H,m), 2.70 and 2.83(3H,s), 3.56 and 3.79(1H,dd,J=5.0-5.9,7.6Hz), 3.94 and 4.44(1H,d,J=10.9-11.2Hz), 4.56 and 4.74(1H,dd,J=6.6-8.9,14.2-16.2Hz), 5.47(1H,brs), 5.85 and 5.96(1H,brs), 6.4-6.9(3H,m), 6.9-7.2(5H,m), 9.01(1H,d,J=7.9Hz)						

Table D-3

Example 29

Synthesis of N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	H	H

Reaction 3

Compound I-b1:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction Time hr	Column sol.	Product	Amount g
0.3	0.31	0.26	0.43	5	20	MC:M 20:1	I-C2	0.43

^{1}H-NMR ($CDCl_3$):δ 0.72,0.79,and 0.92(6H,d,J=6.6Hz), 1.33, 1.34, 1.37, and 1.40(18H,s), 2.1-2.3(1H,m), 2.24 and 2.67(3H,s), 2.6-3.3(4H,m), 4.40 and 4.50(1H,d,J=10.9-11.6Hz), 4.5-4.8(1H,m), 4.8-4.9 and 5.0-5.2(1H,m), 5.49 and 5.98(2H,brs), 6.16(1H,s), 6.31(1H.brd,J=8.3Hz), 6.5-6.8(2H,m), 6.8-7.3(5H,m)

Reaction 4a

Compound I-c2:g	TFA ml	CH_2Cl_2 ml	Reaction Time hr	Column sol.	Amount g	HPLC min
0.35	1.5	3	0.5	CH:M:N 400:10:1	0.24	18.0

EI-MS(M^+):528

^{1}H-NMR($CDCl_3$):δ 0.52, 0.79, and 0.91(6H,d,J=5.0-6.9Hz), 1.33 and 1.39(9H,s), 2.1-2.3(1H,m), 2.24 and 2.36(3H,s), 2.56 and 2.61(3H,s), 2.6-3.2(4H,m), 3.54 and 3.61(1H,dd,J=5.9-6.3,7.3-7.6Hz), 3.78 and 4.58(1H,d,J=10.9Hz), 4.49 and 4.68(1H,dd,J=7.3,14.5Hz), 5.38, 5.58, 5.78, and 5.90(2H,brs), 6.6-7.2(7H,m), 9.07(1H,brd,J=7.6Hz)

Table D-4

Example 30

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	H	H

Reaction 3

Compound I-b1:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.3	0.36	0.26	0.43	5	16	CH:M:N 400:10:1	I-c3	0.42

^{1}H-NMR($CDCl_3$):δ 0.41, 0.67, and 0.86(6H,d,J=6.6Hz), 1.0-1.2(3H,m), 1.36(9H,s), 2.1-2.3(1H,m), 2.51 and 2.76(3H,s), 2.6-3.0 and 3.0-3.2(6H,m), 4.1-4.3(1H,m), 4.4-4.6(1H,m), 4.9-5.0 and 5.1-5.3(1H,m), 5.13(2H,s), 5.35(1H,brs), 5.76(2H,brs), 6.1-6.2 and 6.4-7.4(13H,m)

Reaction 4a

Compound I-c3:g	$Pd(OH)_2$ g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.37	0.07	5	1	CH:M:N 400:10:1	0.24	18.5

EI-MS(M^+):542

^{1}H-NMR($CDCl_3$):δ 0.39, 0.77, and 0.90(6H,d,J=6.3-6.9Hz), 1.05 and 1.16(3H,t,J=6.9Hz), 1.32 and 1.39(9H,s), 2.1-2.3(1H,m), 2.3-3.2(6H,m), 2.43 and 2.46(3H,s), 3.5-3.7(1H,m), 3.76 and 4.58(1H,d,J=10.9-11.5Hz), 4.47 and 4.68(1H,dd,J=7.0,13.9Hz), 5.42, 5.73, and 6.00(2H,brs), 6.6-7.2(7.8H,m), 8.74(0.2H,d,J=7.9Hz)

Table D-5

Example 31

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	H	Me

Reaction 1

Compound T2:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.07	1.36	1.31	1.79	43	2.5	EA:H 1:1	I-a2	2.11

EI-MS(M^+):497
^{1}H-NMR ($CDCl_3$):δ 0.84 and 0.89(6H,d,J=6.6Hz), 1.36(9H,s), 2.12-2.30(1H,m), 2.71, 2.73, and 2.74(6H,s), 2.70-3.00(2H,m), 4.04(1H,d,J=11.2Hz), 4.40-4.58(1H,m), 4.82-4.86(1H,m), 5.19(2H,s), 5.70-5.80(1H,m), 6.43(1H,d,J=7.9Hz), 6.53(1H,d,J=8.2Hz), 6.80(1H,d,J=8.2Hz), 7.04(1H,s), 7.30-7.42(5H,m)

Reaction 2

Compound I-a2:g	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
2.01	200	50	2	C:M 20:1	I-b2	1.43

EI-MS(M^+):363
^{1}H-NMR($CDCl_3$):δ 0.67 and 0.83(6H,d,J=5.9Hz), 1.37(9H,s), 1.84-2.02(1H,m), 2.31(3H,s), 2.73(1H,d,J=5.9Hz), 2.74(3H,d,J=5.0Hz), 2.90-3.08(2H,m), 4.52(1H,ddd,J=7.2,7.2,7.2Hz), 5.51(1H,brs), 5.98(1H,d,J=3.6Hz), 6.61(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.04(1H,d,J=2.0Hz), 7.68(1H,d,J=7.9Hz)

Table D-6

Example 31(Continued from Table D-5)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

Reaction 3

Compound I-b2:mg	Compound P1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
400	387	337	0.46	11	13	EA:H 2:1	I-c4	652

EI-MS(M^+):628

^{1}H-NMR ($CDCl_3$):δ 0.75, 0.77, 0.88, and 1.00(total 6H,d,J=5.3-6.3Hz), 1.36, 1.37 and 1.39(total 18H,s), 2.16-2.30(1H,m), 2.72(3H,d,J=4.6Hz), 2.70-3.22(7H,m), 4.38-4.80, and 5.10-5.22(total 3H,m), 5.28 and 5.32(total 1H,brs), 5.54-5.64(1H,m), 6.04-6.12(1H,m), 6.58-7.22(7H,m)

Reaction 4a

Compound I-c4:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
564	2	8	1.5	MC:M 20:1	367	18.9

EI-MS(M^+):528

^{1}H-NMR ($CDCl_3$):δ 0.72,0.81 and 0.92(total 6H,d,J=6.3-6.6Hz), 1.36 and 1.38(total 9H,s) ,2.20-2.40(1H,m), 2.50-3.24(10H,m), 3.59(2/3H,dd,J=5.6,7.6Hz), 3.73(1/5H,d,J=7.0Hz), 3.80(1/3H,dd,J=6.0,8.3Hz), 3.95(4/5H,d,J=8.9Hz), 4.40-4.54(2/5H,m), 4.63(3/5H,dd,J=6.6,14.2Hz), 5.65 and 5.78(total 1H,d,J=3.8-4.3Hz), 6.60(1/4H,d,J=8.3Hz), 6.70-7.16(7H,m), 9.07(3/4H,d,J=8.3Hz)

Table D-7

Example 32

Synthesis of N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	H	Me

Reaction 3

Compound I-b2:mg	Compound P2:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
400	392	337	0.46	11	15	EA:H 1:1	I-c5	590

EI-MS(M^+):642

^{1}H-NMR($CDCl_3$):δ 0.72, 0.80, and 0.91(total 6H,d,J=6.2-6.6Hz), 1.23, 1.34, 1.37 and 1.39(total 18H,s), 2.06-2.30(1H,m), 2.25, 2.68, 2.75 and 2.86(total 6H,s), 2.79(3H,d,J=4.6Hz), 2.50-3.24(4H,m), 4.38-4.92 and 5.08-5.20(total 3H,m), 5.53 and 6.00(total 1H,brs), 5.88 and 6.21(total 1H,d,J=5.0-8.3Hz), 6.52-7.22(7H,m)

Reaction 4a

Compound I-c5:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
492	2	8	1	CH:M 20:1	305	18.9

EI-MS(M^+):542

^{1}H-NMR($CDCl_3$):δ 0.57,0.79 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.35 and 1.38(total 9H,s), 2.20-2.34(1H,m), 2.25 and 2.40(total 3H,s), 2.63 and 2.64(total 3H,s), 2.71 and 2.73(total 3H,d,J=4.3-4.6Hz), 2.60-3.10(4H,m), 3.55(1/2H,t,J=7.0Hz), 3.67(1/2H,t,J=6.9Hz), 3.81(1/2H,d,J=10.9Hz), 5.30-5.72(2H,m), 6.58-7.20(7H,m), 9.13(1/2H,d,J=8.6Hz)

Table D-8

Example 33

Synthesis of N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	H	Me

Reaction 3

Compound I-b2:mg	Compound P3:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
490	559	414	0.45	8	13	EA:H 1:1	I-c6	747

^{1}H-NMR($CDCl_3$):δ 0.40, 0.47, 0.67 and 0.86(total 6H,d,J=6.3-6.9Hz), 1.06-1.22(3H,m), 1.36 and 1.38(total 9H,s), 2.10-2.26(1H,m), 2.49 and 2.78(total 3H,s), 2.79 and 2.73(total 3H,d,J=4.6-4.9Hz), 2.60-3.40(6H,m), 4.28-4.44(2H,m), 4.90-5.16(3H,m), 5.40-5.68(2H,m), 6.38-7.42(12H,m)

Reaction 4b

Compound I-c6:mg	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min
660	66	10	12	CH:M:N 10:1:0.1	184	19.6

EI-MS(M^+):556

^{1}H-NMR($CDCl_3$):δ 0.40, 0.77 and 0.89(total 6H,d,J=6.6Hz), 1.06 and 1.19(total 3H,t,J=7.0-7.3Hz), 1,34 and 1.38(total 9H,s), 2.10-2.28(1H,m), 2.48(3H,s), 2.30-3.20(6H,m), 2.73 and 2.74(total 3H,d,J=4.6Hz), 3.58-3.70(1H,m), 3.76(3/10H,d,J=11.2Hz), 4.38(7/10H,dt,J=4.9,7.3Hz), 4.50(7/10H,d,J=11.2Hz), 4.56(3/10H,dt,J=7.3,7.9Hz), 5.72-5.90(2/3H,m), 6.60-7.18(8H,m), 8.68(1/2H,d,J=7.9Hz)

Table D-9

Example 34

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	Me	H

Reaction 3

CompoundI I-b3:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.600	0.638	0.549	0.46	16	16	H:EA=2:1	I-c7	0.729

Reaction 4a

Compound I-c7:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.635	3.00	15	2	MC:M:H 10:1:1	0.413	19.6

EI-MS(M^+):542

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.58, 0.81, 0.82 and 0.93(6H, d, J=6.4-6.9 Hz), 1.32 and 1.40(9H, s), 2.20-2.34(1H, m), 2.22 and 2.24(3H, s), 2.50 and 2.93(3H, s), 2.84 and 3.04(3H, s), 2.52 and 2.74(3H, d, J=6.5-6.9Hz), 3.18-3.41(1H, m), 3.42 and 3.62(1H, t, J=5.0-6.8Hz), 5.03 and 5.13(1H, d, J=10.7-10.9 Hz), 5.42-5.49(1H, m), 5.38 and 6.01(1H, brs), 6.38 and 6.62(1H, d, J=8.0Hz), 6.78-6.99(3H, m), 7.04-7.12(3H, m)

Table D-10

Example 35

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	Me	H

Reaction 3

Compound I-b3:g	Compound P4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.460	0.520	0.420	0.53	10.0	17	H:EA 2:1	I-c8	0.300

Reaction 4a

Compound I-c8:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.300	1.44	1.44	2	MC:M:H 10:1:1	0.200	20.2

EI-MS(M^+):556

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.54~1.1(6H, m and d, J=6.3Hz), 1.35 and 1.39(9H, s), 2.48 and 2.81(3H,s) 2.97 and 3.07(3H, s), 2.21 ~ 3.76(7H, m), 5.55~5.02(3H,m), 6.37 and 6.61(1H, d, J=8.3Hz), 6.78~7.21(6H, m)

Table D-11

Example 36

Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH-Me

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	Me	Me

Reaction 1

Compound T5:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.500	1.960	2.030	2.37	30.00	21	EA:H:MC 3:2:2	I-a4	2.200

Reaction 2

Compound I-a4:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
2.200	0.220	50.00	1	Not purified	I-b4	1.400

Reaction 3

CompoundI I-b4:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.430	0.420	0.400	0.47	10.00	19	MC:M:H 10:1:3	I-c9	0.500

Reaction 4a

Compound I-c9:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.500	2.50	2.50	1	MC:M:H 15:1:2	0.320	19.8

EI-MS(M^+):542

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.51~0.92(6H, d, J=6.6Hz), 1.32 and 1.37(9H, s), 2.24(2H, d, J=8.3Hz) 2.52 and 2.82 (3H, s) 2.18 ~ 3.89 (7H, m), 3.04 and 3.13 (3H, s), 5.42~4.82(3H,m), 6.41 and 6.63(1H, d, J=8.2Hz), 6.78~7.19(6H, m)

Table D-12

Example 37

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH-Me

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	Me	Me

Reaction 3

CompoundI I-b4:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.430	0.440	0.400	0.47	10.00	19	EA:H:MC 2:1:1	I-c10	0.500

Reaction 4a

Compound I-c10:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.500	2.50	2.50	1	MC:M:H 15:1:2	0.260	20.3

EI-MS(M^+):556

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.76~0.92(6H, m and d, J=6.3Hz), 1.34 and 1.39(9H, s), 2.25(3H, d, J=11.6Hz), 2.52 and 2.82(3H, s), 2.95 and 3.07(3H, s), 2.21 ~ 3.64(5H, m), 2.71 and 2.76(3H, d, J=4.3Hz), 5.42~5.01(3H,m), 6.37 and 6.54(1H, d, J=8.2Hz), 6.78~7.11(6H, m)

Table D-13

Example 38

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	Me	Me

Reaction 3

CompoundI I-b4:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.450	0.560	0.460	0.50	10.00	19	EA:H:MC 2:1:1	I-c11	0.450

Reaction 4a

Compound I-c11:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.450	0.050	15.00	1	MC:M:H 15:1:2	0.220	21.4

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.54~1.1(6H, m and d, J=6.3Hz), 1.26 and 1.34(9H, s), 2.77(3H,s), 2.97(3H, s), 3.07(3H, s), 2.12 ~ 3.72(7H, m), 5.38~5.21(3H,m), 6.37 and 6.54(1H, d, J=8.3Hz), 6.78~7.21(6H, m)

Table D-14

Example 39

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	Et	H

Reaction 1

Compound T7:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.000	5.720	5.510	6.02	100	24	EA:H:MC 2:1:1	I-a5	3.310

Reaction 2

Compound I-a5 :g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
3.100	0.300	70.00	1	MC:M:H 15:1:2	I-b5	1.600

Reaction 3

Compoun d I-b5:g	Compoun d P1:g	CMPI g	TEA ml	THF ml	Reactio n time hr	Column sol.	Produc t	Amount g
0.400	0.430	0.370	0.46	10.00	19	EA:H:MC 2:1:1	I-c12	0.380

Reaction 4a

Compound I-c12:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.380	1.50	1.50	2	MC:M:H 15:1:2	0.150	20.5

EI-MS(M^+):542
^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.72~1.33(m, 9H), 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz), 2.70 and 2.90(3H, s), 2.21 ~ 3.70 (7H, m) 4.92~5.23(3H, m), 6.41 and 6.61(1H, d, J=7.9Hz), 6.80~7.19(6H, m)

Table D-15

Example 40

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	Et	H

Reaction 3

Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.440	0.450	0.380	0.48	10.00	19	EA:H:MC 2:1:1	I-c13	0.220

Reaction 4a

Compound I-c13:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.220	1.50	1.50	2	MC:M:H 15:1:2	0.130	21.0

EI-MS(M^+):447

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.72~0.95(6H, d, J=6.6Hz), 1.13~1.32(3H, m) 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz) 2.21 ~ 3.96 (7H, m), 2.75 and 3.08 (3H, s), 4.92~5.40(3H, m), 6.41 and 6.63(1H, d, J=7.9Hz), 6.78~7.19(6H, m)

Table D-16

Example 41

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	Et	H

Reaction 3

Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.490	0.480	0.420	0.52	10.00	19	EA:H:MC 2:1:1	I-c14	0.260

Reaction 4a

Compound I-c14:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.260	0.030	10.00	2	MC:M:H 15:1:2	0.120	21.9

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.74~1.26(12H, m), 1.34 and 1.39(9H, s), 2.84 and 2.67(3H, s), 2.22~3.81(8H, m), 4.7~5.22(3H, m), 6.43 and 6.59(1H, d, J=7.9Hz), 6.81~7.19(6H, m)

Table D-17

Example 42

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	Et	Me

Reaction 1

Compound T8:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.20	4.80	4.62	6.31	75	13	EA:H 1:1	I-a6	4.33

EI-MS(M^+):585

^{1}H-NMR($CDCl_3$):δ 0.53, 0.80, 0.82 and 0.89(total 6H,d,J=6.3-6.6Hz), 0.96-1.30(3H,m), 1.34,1.36 and 1.36(total 9H,s), 2.20-2.40(1H,m), 2.46 and 2.75(total 3H,d,J=4.6Hz), 2.57 and 2.95(total 3H,s), 2.66-3.68(4H,m), 4.33, 4.45 and 4.59(total 1H,d,J=10.6Hz), 4.78-4.92(1H,m), 4.96-5.36(3H,m), 6.30-7.12(4H,m), 7.30-7.44(5H,m)

Reaction 2

Compound I-a6:g	$Pd(OH)_2$ mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
2.81	280	60	1.5	CH:M 10:1	I-b6	2.10

EI-MS(M^+):391

^{1}H-NMR($CDCl_3$):δ 0.34, 0.73, 0.90 and 0.96(total 6H,d,J=6.3-6.9Hz), 1.13 and 1.18(total 3H,t,J=6.9Hz), 1.36 and 1.37(total 9H,s), 1.60-1.80(1/2H,m), 2.14 and 2.27(total 3H,s), 2.10-2.30(1/2H,m), 2.58(1/2H,d,J=9.6Hz), 2.92-3.64(9/2H,m), 4.50-4.60(1/3H,m), 4.96-5.10(2/3H,m), 5.10-5.30(1H,m), 6.48(2/3H,brs), 6.54(1/3H,d,J=7.9Hz), 6.57(2/3H,d,J=7.9Hz), 6.79(1/3H,dd,J=2.0,7.9Hz), 6.91(2/3H,dd,J=2.0,7.9Hz), 7.00(1/3H,d,J=2.0Hz), 7.10(2/3H,d,J=2.0Hz), 8.24-8.34(1/3H,m)

Table D-18

Example 42(Continued from Table D-17)

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

Reaction 3

Compound I-b6:mg	Compound P1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
457	397	359	0.39	6	22	MC:M 20:1	I-c15	724

EI-MS(M^+):657

^{1}H-NMR($CDCl_3$):δ 0.72,0.78,0.82 and 0.89(total 6H,d,J=6.3-6.9Hz),1.08 and 1.16(total 3H,t,J=6.9Hz),1.33,1.36,1.38,and 1.39(total 18H,s),2.14-2.28(1H,m),2.54 and 2.98(total 3H,s),2.65 and 2.75(total 3H,d,J=4.6-4.9Hz),2.60-3.64(6H,m),4.58-5.18(4H,m),6.32-6.72(2H,m),6.90-7.18(5H,m)

Reaction 4a

Compound I-c15:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
651	3	7	1	MC:M:H 20:1:1	354	21.5

EI-MS(M^+):556

^{1}H-NMR($CDCl_3$):δ 0.67,0.82 and 0.92(total 6H,d,J=6.6Hz),1.10 and 1.15(total 3H,t,J=6.9Hz),1.34 and 1.39(total 9H,s),2.24-2.44(1H,m),2.67 and 2.76(total 3H,d,J=4.3-4.9Hz),2.73 and 3.05(total 3H,s),2.50-3.90(7H,m),4.94-5.08(2H,m),6.36-7.18(7H,m)

Table D-19

Example 43

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Me	Me	Et	Me

Reaction 3

Compound I-b6:mg	Compound P2:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
465	424	365	0.40	6	21	EA:H 2:1	I-c16	759

^{1}H-NMR($CDCl_3$):δ 0.45, 0.73, 0.82 and 0.89(total 6H,d,J=6.4-6.9Hz), 1.02(3H,t,J=6.6Hz), 1.29, 1.36, 1.37, 1.39 and 1.42(total 18H,s), 2.20-2.30(1H,m), 2.36, 2.71, 2.93 and 3.67(total 6H,s), 2.77 and 2.90(total 3H,d,J=4.6-4.9Hz), 2.60-3.44(6H,m), 4.80-5.28(total 3H,m), 6.09(1H,d,J=4.0Hz), 6.19 and 6.35(total 1H,dd,J=1.3,7.3Hz), 6.51(1/2H,s), 6.60 and 6.69(total 1H,d,J=7.3Hz), 6.94-7.16(13/2H,m)

Reaction 4a

Compound I-c16:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
651	3	7	1	MC:M:H:N 10:1:1:0.1	457	22.1

EI-MS(M^+):570

^{1}H-NMR($CDCl_3$):δ 0.72, 0.83 and 0.92(total 6H,d,J=6.6Hz), 1.14 and 1.16(total 3H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.23 and 2.27(total 3H,s), 2.20-2.40(1H,m), 2.55(1H,d,J=6.3Hz), 2.64-2.88(7H,m), 2.99(1H,dd,J=9.2,14.9Hz), 3.23(1H,dd,J=6.9,14.9Hz), 3.40-3.74(3H,m), 5.00-5.12(2H,m), 6.40 and 6.57(total 1H,d,J=7.9-8.2Hz), 6.44(1/2H,brs), 6.80(1/2H,dd,J=1.6,7.9Hz), 6.90-7.18(11/2H,m)

Table D-20

Example 44

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Me	Et	Me

Reaction 3

Compound I-b6:mg	Compound P3:mg	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
640	675	501	0.55	9	17	EA:H 1:1	I-c 17	963

^{1}H-NMR($CDCl_3$):δ 0.71, 0.78, 0.88, 1.07 and 1.09(total 6H,d,J=6.3-6.9Hz), 0.98 and 1.18(total 3H,t,J=6.9Hz), 1.29, 1.35 and 1.39(total 9H,s), 2.14-2.30(1H,m), 2.48-3.56(14H,m), 4.78(1H,d,J=10.6Hz), 4.86-5.24(3H,m), 5.98-6.10(3/2H,m), 6.21(1H,s), 6.59 and 6.64(total 1H,d,J=7.9Hz), 6.84-7.20(11/2H,m), 7.30-7.44(5H,m)

Reaction 4b

Compound I-c17:mg	$Pd(OH)_2$mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min
870	87	15	15	CH:M 10:1	252	22.9

EI-MS(M^+):584

^{1}H-NMR($CDCl_3$): δ 0.73, 0.82 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.01, 1.06, 1.13 and 1.16(total 6H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.20-3.04(5H,m), 2.67 and 2.78(total 3H,s), 2.69 and 2.74(total 3H,d,J=4.6-4.9Hz), 3.26(1H,dd,J=7.9,14.2Hz), 3.45(1H,dd,J=8.9,13.2Hz), 3.54-3.74(2H,m), 4.94-5.12(5/2H,m), 5.38-5.46(1/2H,m), 6.42 and 6.57(total 1H,d,J=7.9-8.3Hz), 6.80-7.16(6H,m)

Table D-21

Example 45

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	H	H

Reaction 1

Compound T1:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.3	4.29	4.0	4.3	80	2	EA:H 3:1	I-a7	6.5

^{1}H-NMR($CDCl_3$):δ 0.7-1.0(9H,m), 1.2-1.4(9H,m), 2.2-2.4(1H,m), 2.8-3.0(1H,m), 3.0-3.15(1H,m), 3.2-3.35(2H,m), 3.6-3.7(1H,brd,J=10.9Hz), 4.45-4.6(1H,m), 5.04(1H,brs), 5.15(1H,s), 5.15-5.25(1H,m), 6.02(1H,brs), 6.47(1H,brd,J=7.3Hz), 6.86(1H,brd,J=7.3Hz), 7.0-7.2(2H,m), 7.3-7.5(5H,m)

Reaction 2

Compound I-a7:g	$Pd(OH)_2$ g	EtOH ml	Reaction time hr	Column sol.	Product	Amount g
6.4	1.2	130	1.5	Not purified	I-b7	4.37

^{1}H-NMR($CDCl_3$): δ 0.63(3H,d,J=6.6Hz), 0.83(3H,d,J=6.6Hz), 1.03(3H,t,J=6.9z), 1.37(9H,s), 1.85-2.05(1H,m), 2.4-2.6(2H,m), 2.86(1H,d,J=4.0Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.55(1H,brs), 6.22(1H,brs), 6.4-6.6(1H,m), 6.64(1H,d,J=7.3Hz), 6.92(1H,brd, J=7.3Hz), 7.05(1H,brs), 7.90(1H,brd,J=8.3Hz)

Table D-22

Example 45(Continued from Table D-21)

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2

Reaction 3

Compound I-b7:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.17	1.06	1.7	4	13	EA:H 1:2	I-c18	0.56

^{1}H-NMR($CDCl_3$):δ 0.3-0.9(9H,m), 1.2-1.5(18H,m), 2.2-2.4(1H,m), 2.6-3.4(6H,m), 3.9-4.1, 4.4-4.8, and 4.8-4.9(3H,m), 5.53(1H,brs), 6.25(1H,brs), 6.25-6.45(2H,m), 6.56(1H,brs), 6.6-6.9(1H,m), 6.9-7.1(3H,m), 7.15-7.3(2H,m), 7.6-7.8(1H,m)

Reaction 4a

Compound I-c18 g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.51	2	4	1	MC:M 20:1	0.36	19.9

EI-MS(M^+):528

^{1}H-NMR($CDCl_3$):δ 0.60(3H,d,J=6.6Hz), 0.8-0.9(6H,m), 1.38(9H,s), 2.2-2.4(1H,m), 2.68(1H,dd,J=7.3,13.5Hz), 2.8-3.0(2H,m), 3.0-3.25(3H,m), 3.71(1H,t,J=6.9Hz), 4.21(1H,brd,J=10.9Hz), 4.4-4.6(1H,m), 5.55(1H,brs), 6.23(1H,brs), 6.64(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.7,7.9Hz), 6.9-7.0(1H,m), 6.97(2H,t,J=8.6Hz), 7.0-7.2(3H,m)

Table D-23

Example 46

Synthesis of N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	H	H

Reaction 3

Compound I-b7:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.0	1.23	1.06	1.7	4	14	MC:M 50:1	I-c 19	0.54

Reaction 4a

Compound I-c19:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.48	2	4	0.5	MC:M 20:1	0.26	20.4

EI-MS(M^+):542

^{1}H-NMR($CDCl_3$):δ 0.57, 0.68, 0.71, and 0.91(6H,d,J=6.6Hz), 0.99 and 1.05(3H,t,J=6.9Hz), 1.37(9H,s), 2.29 and 2.38(3H,s), 2.3-2.5(1H,m), 2.8-3.4(6H,m), 3.52 and 3.60(1H,t,J=6.6Hz), 3.6-3.9(1H,m), 4.5-4.7(1H,m), 5.66, 5.74, 5.83, and 6.25(2H,brs), 6.66.6-7.2(7H,m), 7.61(1H,brd,J=5.4Hz), 9.16(1H,d,J=7.6Hz)

Table D-24

Example 47

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	H	H

Reaction 3

Compound I-b7:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.42	1.06	1.7	4	14	MC:M 50:1	I-c 20	0.86

^{1}H-NMR ($CDCl_3$):δ 0.35-1.2(12H,m), 1.36, 1.38, and 1.40(9H,s), 2.2-2.4(1H,m), 2.7-3.0 and 3.2-3.6(8H,m), 3.7-3.9, 4.1-4.3, 4.4-4.6, and 4.9-5.1(3H,m), 5.1-5.5(3H,m), 6.5-6.7, 6.8-7.0, and 7.0-7.4(12H,m), 7.6-7.8(1H,m).

Reaction 4a

Compound I-c20 g	$Pd(OH)_2$ g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.8	0.16	10	1	MC:M 20:1	0.31	20.6

EI-MS(M^+):556

^{1}H-NMR($CDCl_3$):δ 0.45, 0.63, 0.67,and 0.73(6H,d,J=6.6Hz), 0.8-1.2(6H,m), 1.38(9H,s), 2.1-2.7(3H,m), 2.7-3.3(6H,m), 3.5-3.9(2H,m), 4.4-4.7(1H,m), 5.38(1H,brs), 5.4-5.6(1H,m), 5.9-6.3(1H,m), 6.62(1H,d,J=7.9Hz), 6.7-7.0(3H,m), 7.0-7.2(3H,m), 7.45-7.65(1H,m)

Table D-25

Example 48

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	H	Me

Reaction 1

Compound T2:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.95	6.62	6.57	8.3	120	2	EA:H 3:2	I-a8	9.0

Reaction 2

Compound I-a8:g	$Pd(OH)_2$ g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
8.9	0.90	200	1.5	Not purified	I-b8	6.4

^{1}H-NMR($CDCl_3$):δ 0.64(3H,d,J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.05(3H,t,J=7.1Hz), 1.37(9H,s), 1.90-2.02(1H,m), 2.51(2H,q,J=6.9Hz), 2.73(3H,d,J=4.9Hz), 2.86(1H,d,J=4.3Hz), 2.91-3.07(2H,m), 4.53(1H,dd,J=7.2,15.2Hz), 6.04(1H,brd,J=4.6Hz), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.03(1H,d,J=2.0Hz), 7.88(1H,d,J=8.3Hz)

Table D-26

Example 48(Continued from Table D-25)

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

Reaction 3

Compound I-b8:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.70	1.91	1.72	1.9	7.5	31	MC:M:N 30:1:0.1	I-c21	0.63

Reaction 4a

Compound I-c21:g	TFA ml	CH_2Cl_2 ml	Reaction time min	Column sol.	Amount g	HPLC min
0.54	5	6	15	MC:M:N 40:1:0.1	0.31	21.0

EI-MS(M^+):542

^{1}H-NMR($CDCl_3$):δ 0.67(1H,d,J=6.6Hz), 0.72(1H,d,J=6.3Hz), 0.75(2H,d,J=6.6Hz), 0.92(2H,d,J=6.3Hz), 1.02-1.07(3H,m), 1.37(6H,s), 1.39(3H,s), 2.2-2.6(1H,m), 2.65-2.77(3H,m), 2.8-3.2(4H,m), 3.2-3.4(2H,m), 3.5-3.6(1H,m), 3.72(0.3H,m), 3.94(0.7H,d,J=10.9Hz), 4.45-4.63(1H,m), 5.70-5.85(1H,m), 6.04(0.3H,brs), 6.44(0.7H,brs), 6.6-6.8(2H,m), 6.88-7.20(6H,m), 7.45(0.3H,brd), 9.09(0.7H,d,J=7.9Hz)

Table D-27

Example 49

Synthesis of N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	H	Me

Reaction 3

Compound I-b8:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
2.03	1.60	1.51	2.3	10	24	MC:M:N 30:1:0.1	I-c22	0.44

Reaction 4a

Compound I-c22:g	TFA ml	CH_2Cl_2 ml	Reaction time min	Column sol.	Amount g	HPLC min
0.41	3	4	30	MC:M:N 30:1:0.1	0.23	20.8

EI-MS(M^+):556
^{1}H-NMR($CDCl_3$):δ 0.62(5/3H,d,J=6.6Hz), 0.68(4/3H,d,J=6.6Hz), 0.72(4/3H,d,J=6.6Hz), 0.91(5/3H,d,J=6.3Hz), 1.04(5/3H,t,J=7.3Hz), 1.06(4/3H,t,J=6.9Hz), 1.37(5H,s), 1.38(4H,s), 2.2-2.5(1H,m), 2.30(4/3H,s), 2.43(5/3H,s), 2.67(5/3H,d,J=4.6Hz), 2.71(4/3H,d,J=4.9Hz), 2.8-3.8(58/9H,m), 3.83(5/9H, d,J=10.9Hz), 4.48(1H,m), 5.4-6.2(2H,br), 6.62-6.66(1H,m), 6.8-7.2(6H,m), 7.40(4/9H,brd), 9.21(5/9H,d,J=7.9Hz)

Table D-28

Example 50

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	H	Me

Reaction 3

Compound I-b8:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.52	1.53	1.13	1.23	20	96	EA:H 1:1	I-c23	520

^{1}H-NMR ($CDCl_3$):δ 0.41, 0.57, 0.62 and 0.72(total 6H,d,J=6.3-6.9Hz), 0.80-1.20(total 6H,m), 1.35, 1.38 and 1.40(total 9H,s), 2.22-2.42(1H,m), 2.66(3H,d,J=4.3Hz), 2.74-3.56(8H,m), 4.37(1H,dd,J=7.3,7.9Hz), 5.00-5.48(4H,m), 5.78-6.00(1H,m), 6.50-6.66(1H,m), 6.84-7.44(11H,m)

Reaction 4b

Compound I-c23:mg	$Pd(OH)_2$mg	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
450	45	8	14	MC:M:N 20:1:1	308	21.6

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$):δ 0.47, 0.64, 0.70 and 0.76(total 6H,d,J=6.3-6.6Hz), 0.88-1.24(6H,m), 1.38(9H,s), 2.10-2.64(3H,m), 2.70 and 2.71(total 3H,d,J=4.6Hz), 2.80-3.30(6H,m), 3.58-3.94(2H,m), 4.46(1H,dd,J=7.6-7.9Hz), 5.74-6.08(2H,m), 6.61(1H,d,J=7.9Hz), 6.78-7.20(6H,m), 7.38(1/2H,d,J=6.3Hz), 8.74(1/2H,d,J=7.9Hz)

Table D-29

Example 51

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	Me	H

Reaction 1

Compound T4:g	Compound V2 :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.360	4.500	4.113	3.73	110	20	H:ACT 3:2	I-a9	5.970

Reaction 2

Compound I-a9:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
5.870	1.000	114	1	Not purified	I-b9	3.600

Reaction 3

CompoundI I-b9:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.200	1.350	1.220	1.33	6	18	H:EA 2:1	I-c24	1.160

Reaction 4a

Compound I-c24:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
1.06	5.00	10	1.5	MC:M: H 15:1:2	0.251	19.3

EI-MS(M^+):542

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.30, 0.69, 0.82 and 0.85(6H,d, J=6.4-6.9 Hz), 0.92 and 1.12(3H,t,J=3.4-4.1HZ), 1.35 and 1.37(9H,s), 2.25-2.40(1H,m), 2.56-3.37(5H,m), 2.82 and 3.02(3H,s), 3.60-3.77(2H,m), 4.83-5.38(2H,m), 6.02band 6.18(2H,brs), 6.43 and 6.62(1H,d,J=6.8Hz), 6.82-7.15(6H,m)

Table D-30

Example 52

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	Me	H

Reaction 3

CompoundI I-b9:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.200	1.420	1.220	1.33	7	30	H:EA 1:2	I-c25	0.740

Reaction 4a

Compound I-c25:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.674	3.00	10	2	MC:M:H 10:1:2	0.278	20.0

EI-MS(M^+):556

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.42, 0.78, 0.84 and 0.91(6H,d, J=6.3-6.9 Hz), 0.94 and 1.18(3H, t, J=3.6Hz), 1.35 and 1.37(9H, s), 2.20-2.34(1H,m), 2.29(3H,s), 2.62-3.02(4H,m), 2.93 and 3.04(3H,s), 3.17-3.31(2H,m), 3.45-3.72(1H,m), 5.02 and 5.22(1H, d,J=10.7-10.9 Hz), 5.09 and 5.17(1H,t,J=5.8-6.1Hz), 5.69, 6.07 and 6.57(2H,brs), 6.45 and 6.64(1H,d,J=8.0Hz), 6.78-7.14(6H,m)

Table D-31

Example 53

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	Me	H

Reaction 3

Compound I I-b9:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.020	1.640	1.220	1.33	8	12	MC:M:H 20:1:1	I-c26	1.040

Reaction 4b

Compound I-c26:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.934	0.093	20	3	MC:M:H =15:1:2	0.201 0.103	20.7 22.4

Compound of which yeilded amount was 0.201 g with HPLC retention time of 20.7 min.
EI-MS(M^+):570
^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.42,0.79,0.84 and 0.91(6H,d and m, J=6.3-6.9Hz), 1.02 and 1.11(6H,t,J=3.6Hz), 1.33 and 1.40(3H,s), 2.20-3.36(9H,m), 2.92 and 3.03(3H,s), 3.51-3.75(1H,m), 5.00-5.38(2H,m), 6.02 and 6.58(2H,brs), 6.42-6..62(1H, d, J=8.0Hz), 6.82-7.20(6H, m)

Compound of which yeilded amount was 0.103 g with HPLC retention time of 22.4 min.
EI-MS(M^+):570
^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.13 and 0.79(4H, t, J=3.4 Hz), 0.62 and 0.89(2H, d, J=6.3-6.9Hz), 0.97 and 1.05(6H,t,J=3.6Hz), 1.34 and 1.41(9H,s), 1.92-2.03(1H,m), 2.21-2.60(2H, m), 3.00 and 3.08(3H,s), 2.74-3.25(4H,m), 3.60-3.72(1H,m), 4.62(1H,d,J=8.0Hz), 4.78-4.82(1H,m), 5.18-5.36(2H,m), 6.02(1H,brs), 6.59 and 6.63(1H,d,J=8.0Hz), 6.81-6.98(3H,m), 7.09-7.20(3H,m)

Table D-32

Example 54

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	Me	Me

Reaction 1

Compound T5:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.93	5.0	4.56	5.0	150	12	EA:H 2:1	I-a10	5.02

EI-MS(M^+):525

^{1}H-NMR($CDCl_3$):δ 0.23-1.08(9H,m), 1.34, 1.37, 1.39(9H,s), 2.10-3.56(10H,m), 4.25-5.33(5H,m), 6.00-7.48(9H,m)

Reaction 2

Compound I-a10:g	$Pd(OH)_2$ g	MeOH ml	Reaction time min	Column sol.	Product	Amount g
4.92	0.50	94	40	CH:M:N 100:10:1	I-b10	3.42

^{1}H-NMR($CDCl_3$):δ 0.35, 0.69, 0.88, 0.95(6H,d,J=6.6-6.9Hz), 0.82, 1.03(3H,t,J=7.1Hz), 1.37(9H,s), 1.66-1.83(1H,m), 1.92(2H,dd,J=13.9,6.6Hz), 2.76,2.79(3H,d,J=4.8Hz), 2.89, 2.99(3H,s), 2.92-3.23(2H,m), 4.55, 5.46(1H,dd,J=10.9,4.0Hz), 5.71, 5.89(1H,brs), 6.13, 8.19(1H,m), 6.55, 6.60(1H,d,J=7.9Hz), 6.78, 6.91(1H,dd,J=7.9,1.7Hz), 7.00, 7.07(1H,d,J=1.7Hz)

Table D-33

Example 54(Continued from Table D-32)

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

Reaction 3

Compound I-b10:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.15	1.25	1.13	1.23	20	13	EA:H 2:1	I-c27	434

Reaction 4a

Compound I-c27:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
434	2	2	2.5	EA:EtOH =10:1	86.0 26.8	20.6 22.8

Compound of which yeilded amount was 86.0 mg with HPLC retention time of 20.6 min.

EI-MS(M^+):556

^{1}H-NMR($CDCl_3$):δ 0.27-1.18(9H,m), 1.35,1.39(9H,s), 2.15-3.77(12H,m), 2.84, 3.06(3H,s), 4.87-5.27(2H,m), 5.99-7.20(8H,m)

Compound of which yeilded amount was 26.8 mg with HPLC retention time of 22.8 min.

EI-MS(M^+):556

^{1}H-NMR($CDCl_3$): δ 0.16, 0.40, 0.55, 0.84(6H,d,J=6.3-6.9Hz), 0.83, 1.01(3H,t,J=7.1Hz), 1.36,1.41(9H,s), 2.00-2.21(1H,m), 2.67,2.76(3H,d,J=4.8Hz), 3.05,3.09(3H,s), 2.81-3.30(7H,m), 3.68-3.87(1H,m), 3.72, 3.80(1H,dd,J=7.8,6.1Hz), 4.61, 5.10(1H,d,J=10.7Hz), 4.66, 5.24(1H,dd,J=9.7,6.4Hz), 6.05-7.20(8H,m)

Table D-34

Example 55

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	Me	Me

Reaction 3

Compound I-b10:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.0	1.14	0.98	1.07	17	14	EA:H 2:1	I-c28	322

Reaction 4a

Compound I-c28:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
322	2	2	2	EA:EtOH 10:1	101 38	21.1 22.6

Compound of which yeilded amount was 101 mg with HPLC retention time of 21.1 min.

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$):δ 0.41, 0.79, 0.86, 0.90(6H,d,J=6.3-6.9Hz), 0.94, 1.15(3H,t,J=7.3Hz), 1.34, 1.39(9H,s), 2.27, 2.28(3H,s), 2.71, 2.76(3H,d,J=4.8Hz), 2.15-3.78(9H,m), 2.93,3.08(3H,s), 4.98-5.32(2H,m), 6.03-7.20(8H,m)

Compound of which yeilded amount was 38 mg with HPLC retention time of 22.6 min.

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$): δ 0.10, 0.14, 0.63, 0.85(6H,d,J=6.3-6.9Hz), 0.82, 0.95(3H,t,J=7.1Hz), 1.35, 1.40(9H,s), 2.18, 2.54(3H,s), 2.71, 2.75(3H,d,J=4.8Hz), 2.99, 3.08(3H,s), 1.89-3.27(8H,m), 3.46-3.64(1H,m), 4.54, 5.19(1H,d,J=10.6Hz), 4.66, 5.23(1H,t,J=7.3Hz), 6.51, 6.60(1H,d,J=7.9Hz), 6.07-7.20(7H,m)

Table D-35

Example 56

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	Me	Me

Reaction 3

Compound I-b10:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.0	1.32	0.98	1.07	17	14	EA:H 2:1	I-c29	576

Reaction 4b

Compound I-c29:mg	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min
576	0.05	5	3	EA:EtOH 15:1	192 129	22.0 23.6

Compound of which yeilded amount was 192 mg with HPLC retention time of 22.0 min.

EI-MS(M^+):584

^{1}H-NMR ($CDCl_3$):δ 0.41-1.18(12H,m), 1.35, 1.39(9H,s), 2.12-4.13(14H,m), 2.92,3.08(3H,s), 4.99-5.27(2H,m), 6.00-7.20(8H,m)

Compound of which yeilded amount was 129 mg with HPLC retention time of 23.6 min.

EI-MS(M^+):584

^{1}H-NMR ($CDCl_3$):δ 0.12-1.30(12H,m), 1.36, 1.41(9H,s), 1.93-4.16(14H,m), 2.99,3.07(3H,s), 4.57-5.23(2H,m), 5.40-7.22(8H,m)

Table D-36

Example 57

Synthesis of Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	Et	H

Reaction 1

Compound T7:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
16.000	24.088	23.200	25.32	400.00	60	EA:H:MC 3:2:2	I-a11	16.000

Reaction 2

Compound I-a11:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
9.000	0.900	200.00	2	MC:M:H 15:1:2	I-b11	4.000

Reaction 3

Compound I-b11:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.100	1.150	1.040	1.13	10.00	72	EA:H:MC 3:2:2	I-c30	0.700

Reaction 4a

Compound I-c30:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.650	2.00	2.00	2	MC:M:H 15:1:2	0.180	20.9

EI-MS(M^+):542

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.51, 0.82, 0.87 and 0.94(6H,d,J=6.6~6.9Hz), 0.82~1.31(6H,m), 1.35 and 3.81(9H,s), 2.21~3.82 (9H,m) 4.83~5.30(3H,m), 6.62 and 6.54(1H,d,J=7.9Hz), 6.80~7.21(6H,m)

Table D-37

Example 58

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	Et	H

Reaction 3

Compound I-b11:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.240	1.360	1.170	1.28	10.00	72	EA:H:MC 3:2:2	I-c31	0.300

Reaction 4a

Compound I-c31:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.280	2.00	2.00	2	MC:M:H 15:1:2	0.170	21.2

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.63~1.30(9H, m and d, J=6.3Hz),), 1.34 and 1.39(9H, s), 2.30(3H,s), 2.22~3.90(9H,m), 4.97~5.33(3H,m), 6.43 and 6.62(1H,d,J=7.92), 6.81~7.19(6H, m)

Table D-38

Example 59

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH_2

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	Et	H

Reaction 3

Compound I-b11:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.500	1.980	1.470	1.60	10.00	72	EA:H:MC 3:2:2	I-c32	0.700

Reaction 4b

Compound I-c32:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.650	0.065	10.00	2	MC:M:H 15:1:2	0.240	20.0

EI-MS(M^+):458

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.85~1.27(15H, m), 1.37 and 1.39(9H, s), 2.03~3.63(11H, m), 4.50~4.55(1H, m), 5.02~5.34(2H, m), 6.43 and 6.60(1H, d, J=8.24), 6.81~7.19(6H, m)

Table D-39

Example 60

Synthesis of Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
H	Et	Et	Me

Reaction 1

Compound T8:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
10.000	15.000	14.000	14.96	357	48	H:EA 2:1	I-a12	5.610

Reaction 2

Compound I-a12:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
5.500	1.000	100	2	H:ACT 1:1	I-b12	2.950

Reaction 3

CompoundI I-b12:g	Compoun d P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.900	0.943	0.850	0.93	6	48	CH:M:N 300:10:1	I-c33	0.750

Reaction 4a

Compound I-c33:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.742	4.00	6	2	CH:M:N 300:10:1	0.210	22.0

EI-MS(M^+):570

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.64 and 0.78-1.20(12H, d and m, J=7.0-7.9Hz), 1.24and 1.37(9H, s), 2.20-2.40(1H, m), 2.62-3.08(4H, m), 3.19-3.46(3H, m), 3.57-3.89(2H, m), 4.62-5.11(2H, m), 6.44-6..62(2H, m), 6.79-7.13(5H, m)

Table D-40

Example 61

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Me	Et	Et	Me

Reaction 3

CompoundI I-b12:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.979	1.077	0.925	1.00	24	53	H:EA 2:1	I-c34	0.410

Reaction 4a

Compound I-c34:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.400	4.00	4	1	CH:M:N 200:10:1	0.034	22.4

EI-MS(M^+):584

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.65 and 0.85-1.20(12H, d and m, J=6.8-7.9Hz), 1.34 and 1.39(9H, s), 2.30 and 2.33(3H, s), 2.30-2.48(1H, m), 2.65-3.89(10H, m), 4.90-5.07(2H, m), 5.10-5.23(2H, m), 6.48-6.58(1H, m), 6.63-7.20(6H, m)

Table D-41

Example 62

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R_{31}	R_{32}	R_{33}	R_{34}
Et	Et	Et	Me

Reaction 3

CompoundI I-b12:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.000	1.277	0.945	1.10	6.00	48	MC:M:H 20:1:1	I-c35	0.540

Reaction 4b

Compound I-c35:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.501	0.050	67	2	MC:M:H 25:1:3	0.240	23.2

EI-MS(M^+):598

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.64 and 0.84-0.92(6H, d and m, J=7.9Hz), 1.04, 1.05 and 1.13(6H,t,J=6.3Hz), 1.33 and 1.39(3H, s), 2.21-2.94(6H,m), 3.12-3.80(6H,m), 4.82-5.08(1H, m), 5.13 and 5.20(1H,d,J=9.7Hz), 6.47 and 6.58(1H,d,J=8.8Hz), 6.79-7.19(6H,m)

Table D-42

Example 63

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	H	tBu

Reaction 1

Compound T18:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.58	0.55	0.56	0.61	10	2	EA:H 1:3	I-a13	1.0

Reaction 2

Compound I-a13:g	$Pd(OH)_2$ g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
1.0	0.16	20	5	Not purified	I-b13	0.75

Reaction 3

Compound I-b13:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.37	0.34	0.33	0.38	4	14	MC:M:N 50:1:0.1	I-c36	0.58

Reaction 4a

Compound I-c36:g	TFA ml	CH_2Cl_2 ml	Reaction time min	Column sol.	Amount g	HPLC min
0.49	2	4	30	MC:M:N 30:1:0.1	0.31	23.4

EI-MS(M^+):570

^{1}H-NMR($CDCl_3$):δ 0.72(2H,d,J=6.9Hz), 0.82(1H,d,J=6.6Hz), 0.92-0.96(3H,m), 1.19(3H,s), 1.22(6H,s), 1.37(3H,s), 1.38(6H,s), 2.2-2.4(1H,m), 2.5-3.0(32/5H,m), 3.17(3/5H,dd,J=4.9,13.9Hz), 3.61(3/5H,br), 3.82(2/5H,br), 3.96(3/5H,d,J=10.9Hz), 4.3-4.6(7/5H,m), 5.25(1/3H,s), 5.41(1/3H,br), 5.48(2/3H,s), 6.03(2/3H,br), 6.6-6.8(2H,m), 6.9-7.2(5H,m), 9.00(1H,d,J=7.9Hz)

Table D-43

Example 64

Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2SO_2CH_3$

R_{31}	R_{32}	R_{33}	R_{34}
H	Me	Me	$CH_2SO_2CH_3$

Reaction 1

Compound T17:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.840	0.782	0.753	0.82	10	15	EA:H:MC 3:2:2	I-a14	1.200

Reaction 2

Compound I-a14:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
1.100	0.150	30.00	2	Not purified	I-b14	0.850

Reaction 3

CompoundI I-b14:g	Compound :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.850	0.710	0.572	0.62	10.00	17	EA:H:MC 1:1:1	I-c37	1.020

Reaction 4a

Compound I-c37:g	$Pd(OH)_2$:g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
1.020	0.150	30.00	2	MC:M:H 15:1:2	0.530	20.2

EI-MS(M^+):620

^{1}H-NMR ($CDCl_3$): (two rotamers) δ 0.78(3H, dd, J=6.6, 12.1Hz), 0.91(3H, dd, J=6.6, 11.2Hz), 1.26 and 1.35(9H, s), 2.00(3H,s), 2.55, 2.63, 2.75, 2.84, 2.99 and 3.16(8H,s), 2.21 ~ 5.30(11H, m), 6.43 and 6.55(1H, d, J=7.9Hz), 6.76~7.13(6H, m)

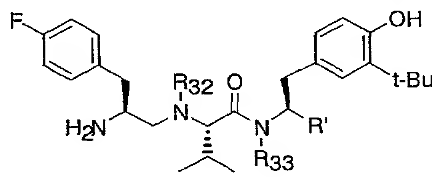
Examples of compounds synthesized according to the scheme 2 are shown in Tables D-44 to D-66.

Table D-44

Example 65

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

Structural Formula of Compounds of Example 65-78



R_{32}	R_{33}	R'
H	Me	$CONH_2$

Reaction 1								
Compound T4:g	Compound V4:g	CMPI :g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
5.78	6.97	7.08	8.05	115	19	EA:H 1:1	I-d1	9.50

^{1}H-NMR($CDCl_3$):δ 0.63, 0.74, 0.89 and 0.94(total 6H,d,J=6.6-6.9Hz), 1.36 and 1.39(total 9H,s), 1.90-2.04(1H,m), 2.80-3.38(2H,m), 2.96 and 3.04(total 3H,s), 4.14-4.22(1/2H,m), 4.40-4.50(1/2H,m), 4.60-4.70(1/2H,m), 4.88-5.40(11/2H,m), 5.88(1/2H,brs), 6.49(1/2H,d,J=7.9Hz), 6.58(1/2H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 7.02-7.14(1H,m), 7.30-7.40(5H,m)

Reaction 2				
Compound I-d1:g	Pd-C g	MeOH ml	Reaction time hr	Crude Compound I-e1 was used in Reaction 3.
4.23	0.50	100	2	

Table D-45

Example 65(Continued from Table D-44)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

Reaction 3								
CompoundI-e1	Compound P5:g	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
Crude compound of Reaction 2	2.37	1.16	1.01	90	1	EA:H 1:1	I-f1	2.08
EI-MS(M^+):600 ^{1}H-NMR($CDCl_3$):δ 0.86 and 1.02(total 6H,d,J=6.6-6.9Hz), 1.31, 1.35, 1.37 and 1.43(total 18H,s), 1.56-1.80(3H,m), 2.58-3.20(7H,m), 3.56-3.66(1H,m), 4.51(1H,d,J=8.6Hz), 5.28(1H,brs), 5.58-5.68(1H,m), 5.93(1H,brs), 6.53(1H,d,J=8.2Hz), 6.82-7.22(7H,m)								

Reaction 7						
Compound I-f1:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
360	3	3	0.5	MC:M:N 10:1:0.1	275	17.8
EI-MS(M^+):500 ^{1}H-NMR($CDCl_3$): δ 0.47, 0.67, 0.92 and 0.95(total 6H,d,J=6.3-6.6Hz), 1.38(9H,s), 1.64-1.80(2H,m), 1.97(1H,dd,J=5.3,11.6Hz), 2.28(1H,dd,J=9.2,13.5Hz), 2.72(1H,dd,J=4.0,13.5Hz), 2.80-3.02(3H,m), 2.94(3H,s), 3.18(1H,dd,J=5.8,14.5Hz), 5.31(1H,brs), 5.55(1H,dd,J=5.9,10.9Hz), 6.00(1H,brs), 6.59(1H,d,J=8.2Hz), 6.89(1H,dd,J=1.9,8.2Hz), 6.97(2H,t,J=8.2Hz), 7.11(2H,t,J=8.2Hz), 7.11(1H,d,J=1.9Hz)						

Table D-46

Example 66

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

R_{32}	R_{33}	R'
Me	Me	$CONH_2$

Reaction 4

Compound I-f1:mg	HCHO ml	$NaBH_3CN$ mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
530	0.38	117	0.10	8	0.5	H:A 1:1	I-g1	532

^{1}H-NMR($CDCl_3$):δ 0.76,0.78 and 0.94(total 6H,d,J=5.2-6.6Hz), 1.37 and 1.38(total 18H,s), 1.58-1.76(4H,m), 1.94-2.30(2H,m), 2.49 and 2.89(total 3H,s), 2.60-3.22(4H,m), 3.58-3.76(1H,m), 4.38 and 4.62(total 1H,d,J=8.6Hz), 5.22-5.30(1H,m), 5.64-5.72(1H,m), 6.07(1H,brs), 6.52-6.62(1H,m), 6.94-7.12(6H,m)

Reaction 7

Compound I-g1:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
465	4	4	1	CH:M:N 10:1:0.1	280	21.5

FAB-MS:515(M+H$^+$)

^{1}H-NMR(CD_3OD):δ 0.14, 0.83, 0.89 and 1.01(total 6H,d,J=6.3-6.6Hz), 1.40 and 1.43(total 9H,s), 1.84-2.18(2H,m), 2.10(3H,s), 2.38-2.50(1H,m), 2.60-3.04(3H,m), 2.91 and 3.06(total 3H,s), 3.18-3.30 and 3.58-3.66(total 3H,m), 4.70 and 5.61(total 1H,dd,J=4.3-5.0,10.9Hz), 6.66 and 6.69(total 1H,d,J=7.9Hz), 6.92 and 6.96(total 1H,dd,J=1.3,7.9Hz), 7.04-7.34(5H,m)

Table D-47

Example 67

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

R_{32}	R_{33}	R'
Ac	Me	$CONH_2$

Reaction 5

Compound I-f1:mg	Ac_2O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
451	3	42.9	5	15	EA:H 1:1	I-h1	306

^{1}H-NMR($CDCl_3$):δ 0.13, 0.60 and 0.87(total 6H,d,J=6.3-6.6Hz), 1.23, 1.26, 1.32 and 1.36(total 18H,s), 2.06-2.30(3H,m), 2.15, 2.16 and 2.31(total 6H,s), 2.48(1H,dd,J=7.9,13.2Hz), 2.74-2.94(2H,m), 3.05 and 3.07(total 3H,s), 3.28-3.42(2H,m), 3.88-4.00(1H,m), 4.88(1H,d,J=8.6Hz), 5.08-5.42(3H,m), 6.31(1H,brs), 6.92(2H,d,J=8.2Hz), 6.98(2H,d,J=8.2Hz), 7.08-7.26(3H,m)

Reaction 6

Compound I-h1:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
412	1	4	1	EA:H 1:1	I-i1	341

^{1}H-NMR($CDCl_3$):δ 0.05, 0.11, 0.52 and 0.61(total 6H,d,J=6.3-6.9Hz), 1.36, 1.37 and 1.42(total 18H,s), 1.70 and 2.05(total 3H,s), 2.00-2.42(2H,m), 2.80-3.40(5H,m), 3.04 and 3.07(total 3H,s), 3.64-3.88(1H,m), 4.76-5.32(5H,m), 5.92(1H,brs), 6.56(1H,d,J=8.2Hz), 6.88-7.30(6H,m)

Table D-48

Example 67(Continued from Table D-47)

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

Reaction 7						
CompoundI-i1 mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
330	3	2	0.5	CH:M 10:1	210	23.4
^{1}H-NMR($CDCl_3$):δ 0.31, 0.69, 0.81 and 0.86(total 6H,d,J=6.3-7.0Hz), 1.38(9H,s), 1.78-1.86(1H,m), 1.85(3H,s), 2.5-2.94(3H,m), 3.05 and 3.07(total 3H,s), 3.04-3.30(1H,m), 3.50-3.84(2H,m), 4.10 and 4.40(total 1H,brs), 4.63 and 4.66(total 1H,brs), 5.06(1H,d,J=10.2Hz), 5.16-5.32(2H,m), 6.54 and 6.65(total 1H,d,J=7.9-8.2Hz), 6.80 and 6.93(total 1H,dd,J=1.5-2.0,7.9-8.2Hz), 6.98-7.14(5H,m)						

Table D-49

Example 68

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

R_{32}	R_{33}	R'
H	Et	$CONH_2$

Reaction 1

Compound T7:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.01	1.25	1.27	1.23	10	19	EA:H 1:1	I-d2	0.75

^{1}H-NMR($CDCl_3$):δ 0.72,0.87, 0.92 and 0.95(total 6H,d,J=6.6-6.9Hz), 1.14-1.30(3H,m), 1.37 and 1.38(total 9H,s), 1.86-1.98(1H,m), 2.76(1/4H,dd,J=6.6,13.8Hz), 3.12(3/4H,dd,J=7.9,13.9Hz), 3.24-3.56(3H,m), 4.20 and 4.33(total 1H,dd,J=6.6-8.6,8.9Hz), 4.60 and 4.71(total 1H,t,J=7.2-7.6Hz), 5.02-5.28(7/2H,m), 5.36(1H,d,J=8.6Hz), 6.26(1/2H,brs), 6.54 and 6.58(total 1H,d,J=7.9-8.2Hz), 6.84-6.92(total 1H,m), 7.08(1H,d,J=1.7Hz), 7.20-7.40(5H,m)

Reaction 2

Compound I-d2:g	Pd-C g	MeOH ml	Reaction time hr	
0.62	0.10	12	1	Crude Compound I-e2 was used in Reaction 3.

Table D-50

Example 68(Continued from Table D-49)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

Reaction 3

Compound I-e2	Compound P5:mg	$NaBH_3CN$ mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
Crude compound of Reaction 2	400	124	0.4	10	1	EA:H 1:1	I-f2	298

^{1}H-NMR($CDCl_3$):δ 0.65, 0.87, 0.90 and 1.02(total 6H,d,J=6.2-6.9Hz), 1.12 and 1.24(total 3H,t,J=6.9-7.3Hz), 1.35, 1.37, 1.38 and 1.41(total 18H,s), 1.50-1.82(3H,m), 2.58-3.64(7H,m), 4.28-4.54(1H,m), 5.04-5.36(2H,m), 6.20-6.32 and 6.52-6.64(2H,m), 6.80-7.12(6H,m)

Reaction 7

Compound I-f2 mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
331	2	3	0.5	MC:M 20:1	234	19.7

EI-MS(M^+):514

^{1}H-NMR($CDCl_3$):δ 0.56, 0.75, 0.94 and 0.96(total 6H,d,J=6.6-6.9Hz), 1.17 and 1.26(total 3H,t,J=6.9-7.3Hz), 1.38(9H,s), 1.50-1.80(2H,m), 1.98(1H,dd,J=8.6,11.2Hz), 2.20-2.50(2H,m), 2.71(1H,dd,J=3.8,13.2Hz), 2.88-3.50(5H,m), 4.54-4.62 and 4.94-5.02(1H,m), 5.21 and 6.40(total 1H,brs), 6.58(1H,d,J=8.2Hz), 6.82-7.18(6H,m)

Table D-51

Example 69

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydrozymethylethyl)-3-methylbutanamide

R_{32}	R_{33}	R′
H	H	CH_2OH

Reaction 1

Compound T19:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.2	1.62	1.65	1.8	50	1.5	EA:H 1:1	I-d3	2.2

^{1}H-NMR($CDCl_3$):δ 0.81(3H,brd,J=6.3Hz), 0.91(3H,d,J=6.6Hz), 1.38(9H,s), 2.0-2.2(1H,m), 2.49(1H,brs), 2.6-2.9(2H,m), 3.5-3.7(2H,m), 3.92(1H,dd,J=5.,7.9Hz), 5.11(2H,s), 5.1-5.3(2H,m), 6.09(1H,brd,J=7.6Hz), 6.57(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.3,7.9Hz), 7.04(1H,d,J=1.3Hz), 7.36(5H,s)

Reaction 2

Compound I-d3 g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
2.2	0.2	48	12	Not purified	I-e3	1.6

^{1}H-NMR($CDCl_3$): δ 0.57(3H,d,J=6.6Hz), 0.89(3H,d,J=6.9Hz), 1.38(9H,s), 2.1-2.3(1H,m), 2.68(1H,dd,J=8.9,13.9Hz), 2.86(1H,dd,J=6.3,13.9Hz), 3.23(1H,d,J=3.6Hz), 3.62(1H,dd,J=6.3,10.9Hz), 3.75(1H,dd,J=3.6,10.9Hz), 4.0-4.2(1H,m), 5.45(1H,brs), 6.61(1H,d,J=7.9Hz), 6.90(1H,dd,J=2.0,7.9Hz), 7.05(1H,d,J=2.0Hz), 7.56(1H,brd,J=6.6Hz)

Table D-52

Example 69(Continued from Table D-51)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

Reaction 3

Compound I-e3:g	Compound P5:g	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.8	0.8	0.33	0.28	25	1.5	CH:M:N 300:10:1	I-f3	1.05

^{1}H-NMR($CDCl_3$):δ 0.69(3H,brd,J=5.9Hz), 0.81(3H,d,J=6.9Hz), 1.38(9H,s), 1.42(9H,s), 1.8-2.0(1H,m), 2.35-3.0(6H,m), 3.0-3.2(1H,m), 3.5-3.9(3H,m), 4.1-4.3(1H,m), 4.5-4.7(1H,m), 5.47(1H,brs), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.36(1H,brd,J=7.6Hz)

Reaction 7

Compound I-f3:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.3	0.5	5	10	CH:M:N 200:10:1	0.21	17.7

^{1}H-NMR($CDCl_3$):0.72(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.8-2.0(1H,m), 2.4-2.9(7H,m), 2.9-3.1(1H,m), 3.50(1H,dd,J=4.6,11.6Hz), 3.66(1H,dd,J=3.0,11.6Hz), 4.1-4.3(1H,m), 6.60(1H,d,J=7.9Hz), 6.92(1H,dd,J=1.7,7.9Hz), 7.0-7.2(6H,m), 7.35(1H,brd,J=8.3Hz)

Table D-53

Example 70

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
Me	H	CH_2OH

Reaction 4

Compound I-f3:g	HCHO ml	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.34	0.23	0.077	0.07	6	1.5	CH:M:N 300:10:1	I-g3	0.33

^{1}H-NMR($CDCl_3$):δ 0.82(3H,d,J=6.3Hz), 0.94(3H,d,J=6.6Hz), 1.37(9H,s), 1.41(9H,s), 2.06(3H,s), 2.1-2.6(4H,m), 2.70(1H,dd,J=8.9,14.2Hz), 2.8-3.0(2H,m), 3.5-3.8(3H,m), 4.2-4.5(2H,m), 5.62(1H,brs), 6.4-6.6(1H,m), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m)

Reaction 7

Compound I-g3:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.3	0.5	5	10	CH:M:N 200:10:1	0.17	20.1

EI-MS(M^+):487
^{1}H-NMR($CDCl_3$):0.79(3H,d,J=6.6Hz), 0.94(3H,d,J=6.6Hz), 1.39(9H,s), 1.9-2.2(1H,m), 2.22(3H,s), 2.2-2.4(3H,m), 2.51(1H,d,J=8.9Hz), 2.6-2.8(2H,m), 2.87(1H,dd,J=6.6,14.2Hz), 3.0-3.2(1H,m), 3.57(1H,dd,J=5.3,10.9Hz), 3.72(1H,dd,J=3.6,10.9Hz), 4.1-4.3(1H,m), 6.19(1H,brd,J=7.3Hz), 6.63(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 6.98(2H,t,J=8.6Hz), 7.0-7.2(3H,m)

Table D-54

Example 71

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R_{32}	R_{33}	R'
H	Me	Me

Reaction 1

Compound T20:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.62	2.22	2.25	2.46	36	16	EA:H 1:1	I-d4	2.74

^{1}H-NMR ($CDCl_3$):δ 0.67, 0.72, 0.89 and 0.95(total 6H,d,J=6.6-6.9Hz), 1.08 and 1.20(total 3H,d,J=6.6-6.9Hz), 1.37 and 1.39(total 9H,s), 1.88-2.02(1H,m), 2.60-2.90(2H,m), 2.89(3H,d,J=3.3Hz), 4.30-4.46(1H,m), 4.90-5.00(1H,m), 5.07(2H,s), 6.48 and 6.59(total 1H,d,J=7.9Hz), 6.78-6.88(1H,m), 7.00-7.08(1H,m), 7.30-7.40(5H,m)

Reaction 2

Compound I-d4:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
2.68	0.25	50	18	MC:M 20:1	I-e4	1.35

^{1}H-NMR($CDCl_3$): δ 0.68, 0.85, 0.95 and 0.99(total 6H,d,J=6.6-6.9Hz), 1.11 and 1.24(total 3H,d,J=6.6Hz), 1.88-2.04(1H,m), 2.58-2.70(2H,m), 2.83 and 2.91(total 3H,s), 3.56-3.64(1H,m), 3.95 and 4.99(total 1H,ddd,J=6.6,6.9,7.6Hz), 6.62 and 6.67(total 1H,d,J=7.9Hz), 6.77 and 6.88(total 1H,dd,J=1.7,7.9Hz), 6.98 and 7.02(total 1H,d,J=1.7Hz)

Table D-55

Example 71(Continued from Table D-54)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

Reaction 3

Compound I-e4:g	Compound P5:g	$NaBH_3CN$ mg	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
1.26	1.58	521	0.453	40	1	EA:H 1:4	I-f4	1.52

^{1}H-NMR ($CDCl_3$):δ 0.74, 0.85 and 0.99(total 6H,d,J=6.6-6.9Hz), 1.16(3H,d,J=6.9Hz), 1.30, 1.41 and 1.44(total 18H,s), 1.50-1.70(3H,m), 2.36-2.90(7H,m), 3.52-3.68(1H,m), 4.54-4.64(1H,m), 5.22-5.38(1H,m), 6.51 and 6.60(total 1H,d,J=7.9Hz), 6.80-7.20(6H,m)

Reaction 7

Compound I-f4:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount mg	HPLC min
330	2	3	0.5	CH:M:N 10:1:0.1	224	20.8

EI-MS(M^+):471

^{1}H-NMR($CDCl_3$): δ 0.80, 0.91 and 0.92(total 6H,d,J=6.6Hz), 1.15(3H,d,J=6.9Hz), 1.38 and 1.41(total 9H,s), 1.64-2.04(4H,m), 2.28-3.14(5H,m), 2.79 and 2.92(total 3H,s), 3.90-4.02 and 5.10-5.24(total 1H,m), 6.62 and 6.65(total 1H,d,J=7.4-7.6Hz), 6.74-7.20(6H,m)

Table D-56

Example 72

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R_{32}	R_{33}	R'
Me	Me	Me

Reaction 4

CompoundI-f4:g	HCHO ml	$NaBH_3CN$ mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
520	0.39	120	0.105	9	0.5	H:EA 2:1	I-g4	404

^{1}H-NMR($CDCl_3$): δ 0.28, 0.74, 0.81 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.17 and 1.21(total 3H,d,J=6.6-6.9Hz), 1.37 and 1.39(total 18H,s), 1.50-1.60(1H,m), 1.58(3H,s), 1.80-2.52(4H,m), 2.60-3.14(3H,m), 2.71(3H,s), 3.62-3.78(1H,m), 4.42-4.54(1H,m), 5.32-5.44(1H,m), 6.50-7.12(8H,m)

Reaction 7

Compound I-g4:mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
386	2	4	0.5	CH:M 10:1	272	24.5

FAB-MS:486($M+H^+$)

^{1}H-NMR($CDCl_3$): δ 0.44, 0.79, 0.93 and 0.96(total 6H,d,J=6.6-6.9Hz), 1.13 and 1.20(total 3H,d,J=6.6-6.9Hz), 1.39 and 1.41(total 9H,s), 1.50-1.98(3H,m), 2.04-2.18(1H,m), 2.13 and 2.30(total 3H,s), 2.32-3.10(5H,m), 2.80 and 2.86(total 3H,s), 4.18-4.28 and 5.24-5.36(total 1H,m), 6.57 and 6.61(total 1H,d,J=7.9Hz), 6.72-7.18(6H,m)

Table D-57

Example 73

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R_{32}	R_{33}	R'
Ac	Me	Me

Reaction 5

Compound I-f4:mg	Ac_2O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
735	4	158	6	16.5	EA:H 1:2	I-h4	489

^{1}H-NMR($CDCl_3$):δ 0.13, 0.54, 0.58 and 0.86(total 6H,d,J=6.3-6.6Hz), 1.13 and 1.15(total 3H,d,J=6.3Hz), 1.30, 1.33, 1.36 and 1.42(total 18H,s), 1.69, 2.08, 2.13 and 2.31(total 6H,s), 2.02-2.84(5H,m), 2.91 and 2.96(total 3H,s), 3.14-3.40(2H,m), 3.82-4.04(1H,m), 4.70-5.28(2H,m), 6.88-7.30(7H,m)

Reaction 6

Compound I-h4:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
470	1	6	1	Not purified	I-i4	440

^{1}H-NMR($CDCl_3$):δ 0.11, 0.12, 0.51 and 0.64(total 6H,d,J=5.9-6.6Hz), 1.09 and 1.13(total 3H,d,J=6.3-6.6Hz), 1.37, 1.38, 1.40 and 1.43(total 18H,s), 1.66 and 2.03(total 3H,s), 2.00-2.44(3H,m), 2.62-2.72(2H,m), 2.68 and 2.92(total 3H,s), 2.88-3.40(2H,m), 3.72-3.88(1H,m), 4.52-5.32(2H,m), 6.52-7.34(7H,m)

Table D-58

Example 73(Continued from Table D-57)

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

Reaction 7						
Compound I-i4 mg	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column sol.	Amount mg	HPLC min
351	2	2	0.5	MC:M:H 20:1:1	233	27.7
^{1}H-NMR($CDCl_3$): δ 0.27, 0.69, 0.83 and 0.87(total 6H,d,J=6.3-6.9Hz), 1.11(3H,d,J=6.6Hz), 1.39 and 1.40(total 9H,s), 1.78 and 1.83(total 3H,s), 1.80-2.04(1H,m), 2.50-2.74(4H,m), 2.82 and 2.93(total 3H,s), 3.28-3.64(2H,m), 4.00-4.24(1H,m), 4.62 and 4.74(total 1H,s), 4.64-5.10(1H,m), 4.97 and 5.13(total 1H,d,J=10.6-10.9Hz), 6.60-7.18(7H,m)						

Table D-59

Example 74

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
H	H	Me

Reaction 1

Compound T21:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
3.000	4.350	4.400	6.00	80	5	H:EA:MC 5:1:1	I-d5	4.000

Reaction 2

Compound I-d5:g	$Pd(OH)_2$: g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
4.000	0.400	100	1	MC:Me:H 10:1:1	I-e5	1.200 and 0.500 (diastereomers)

Reaction 3

Compound I-e5:g	Compound P5:g	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column . sol	Product	Amoun t g
1.200	1.100	0.490	0.30	30	2	H:EA:M C 3:2:2	I-f5	0.730
0.480	0.628	0.207	0.3	10	2	H:EA 1:1		0.620

Table D-60

Example 74(Continued from Table D-59)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

Reaction 7						
Compound I-f5:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.500	2.00	2	1	MC:M:H 10:1:1	0.320	20.7
0.113	1.00	2	1	CH:M:N 300:10:1	0.063	20.4

Compound of which yielded amount was 0. 320 g with HPLC retaintion time of 20.7 min.
EI-MS(M^+):457
^{1}H-NMR($CDCl_3$) :δ 0.73(3H, d, J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.08(3H,d, J=6.3Hz), 1.37(9H,s), 1.81~2.00(1H,m), 2.28-2.80(9H,m), 2.90-3.00(1H,m), 4.21~4.38 (1H,m), 6.68(1H,d,J=8.2Hz), 6.83~7.18(6H,m)
Compound of which yielded amount was 0.063 g with HPLC retention time of 20.4 min.
EI-MS(M^+):457
^{1}H-NMR($CDCl_3$):δ 0.88 and 0.92(6H,d,J=6.9Hz), 1.14(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.10(1H,m), 2.18-2.44(3H,m), 2.84-2.96(4H,m), 3.63-3.75(1H,m), 4.22-4.31(1H,m), 6.60(1H,d,J=6.8Hz), 6.86-7.26(6H, m)

Table D-61

Example 75

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
Me	H	Me

Reaction 4

CompoundI I-f5:g	HCHO ml	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.400	0.32	0.093	0.30	10	2	H:EA:MC 3:1:1	I-g5	0.300
0.500	0.380	0.118	0.10	9	2	H:EA:MC 2:1:1		0.320

Reaction 7

Compound I-g5:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.240	1.00	1	1	MC:M:H 10:1:1	0.140	23.0
0.320	2.00	4	1	CH:M:N 300:10:1	0.226	22.5

Compound of which yielded amount was 0.140 g with HPLC retention time of 23.0 min.
EI-MS(M^++1):472
^{1}H-NMR($CDCl_3$) : δ 0.82(3H, d, J=6.6Hz), 0.93(3H,d,J=6.6Hz), 1.29(3H,d, J=6.3Hz), 1.38(9H,s), 2.03-2.80(11H,m), 2.20(3H,s), 3.00-3.14(1H,m), 4.33~4.40(1H,m), 5.64(1H,d,J=7.7Hz), 6.68(1H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 6.95~7.18(5H,m)

Compound of which yielded amount was 0.226 g with HPLC retention time of 22.5 min.
EI-MS(M^+):471
^{1}H-NMR($CDCl_3$): δ 0.68 and 0.95(6H, d, J=6.6Hz), 1.15(3H,d, J=6.6Hz), 1.37(9H,s), 2.01-2.17(1H,m), 2.21(3H,s), 2.32-2.49(4H,m), 2.64-2.72(3H,m), 3.08-3.10(1H,m), 4.22-4.32(1H,q,J=2.5Hz), 5.60(1H,d,J=6.8Hz), 6.65 and 6.84(2H,d,J=7.9Hz), 6.94-7.00(3H,dd,J=6.3,11.2Hz), 7.13-7.18(2H,m)

Table D-62

Example 76

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
Ac	H	Me

Reaction 5

Compound I-f5:g	Ac_2O ml	DMAP ml	pyridine ml	Reaction time hr	Column. sol	Product	Amount g
0.630	3.00	0.21	4.50	16	H:EA:MC 3:2:2	I-h5	0.560

Reaction 6

Compound I-h5:g	NaOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.540	2.00	4.00	1	Not purified	I-i5	0.430

Reaction 7

Compound I-i5:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.430	2.00	2.00	1	MC:M:H 10:1:1	0.185	22.5

EI-MS(M^{+}+1):500
^{1}H-NMR($CDCl_3$) : δ 0.70(3H, d, J=5.6Hz), 0.84(3H,d, J=6.6Hz), 1.05(3H,d, J=6.6Hz), 1.37(9H,s), 1.78-1.96(2H,m), 1.90(3H,s), 2.43-2.74(4H,m), 3.07-3.32(2H,m), 3.46-3.56(1H,m), 3.59(1H,d,J=14.5Hz), 4.10-4.72(3H,m), 4.71(2H,s), 6.18-6.22(2H,br), 6.63-6.78(2H,m), 6.95-7.18(5H,m)

Table D-63

Example 77

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-N,3-dimethylbutanamide

R_{32}	R_{33}	R'
Me	Me	CH_2OH

Reaction 1

Compound T23:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.928	1.470	1.497	1.64	39	15	H:EA:M 2:3:1	I-d6	1.170

Reaction 2

Compound I-d6:g	Pd-C g	MeOH ml	Reaction time hr	Column. sol	Product	Amoun t g
1.170	0.220	25	1	Not purified	I-e6	0.836

Reaction 3

CompoundI I-e6:g	Compound P5:g	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reactio n time hr	Column. sol	Product	Amou nt g
0.836	0.997	0.329	0.28	25	1	MC:M:H 15:1:1	I-f6	1.20 0

Reaction 4

CompoundI I-f6:g	HCHO ml	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.530	0.400	0.119	0.10	9	2	H:ACT 2:1:	I-g6	0.341

Reaction 7

Compound I-g6:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.225	2.5	3	1	CH:M:N 300:10:1	0.100	24.3

EI-MS(M^+):471

^{1}H-NMR($CDCl_3$): δ 0.12, 0.79,0.84 and 0.98(6H,d,J=6.6-6.8Hz), 1.20(9H,s), 2.02-3.00(10H,m), 2.18 and 2.58(3H,s), 2.84 and 2.87(3H,s), 3.61-3.82(3H,m), 4.01-4.11 and 4.89-4.97(1H,m), 6.52 and 6.63(2H,d,J=8.1Hz), 6.72and 6.89(1H,d,J=7.9Hz), 6.93-7.14(4H, m)

Table D-64

Example 78

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
Me	H	CH_2NH_2

Reaction 1

Compound T22:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.89	0.90	0.92	0.89	13	20	MC:M:N 100:3:0.1	I-d7	1.40

^{1}H-NMR($CDCl_3$):δ 0.80(3H,d,J=6.6Hz), 0.91(3H,d,J=6.6Hz), 1.37(9H,s), 1.42(9H,s), 2.00-2.15(1H,m), 2.55-2.90(2H,m), 3.10-3.30(2H,m), 3.90-4.20(2H,m), 4.80-4.90(1H,m), 5.11(2H,brs), 5.20-5.40(1H,m), 6.35-6.50(1H,m), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd, J=1.3,7.9Hz), 7.02(1H,1.3Hz), 7.36(5H,brs)

Reaction 2

Compound I-d7:g	Pd-C g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
1.40	0.40	40	16	MC:M:N 100:5:0.1	I-e7	0.89

^{1}H-NMR($CDCl_3$):δ 0.56(3H,d,J=6.9Hz),0.88(3H,d,J=6.9Hz), 1.38(9H,s), 1.43(9H,s), 2.10-2.30(1H,m), 2.65-2.85(2H,m), 3.15-3.35(3H,m), 4.15-4.30(1H,m), 4.95-5.05(1H,m), 6.62(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.01(1H,d,J=2.0Hz), 7.43(1H,d,J=8.3Hz)

Table D-65

Example 78 (Continued from Table D-64)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Reaction 3

Compound I -e7:g	Compound P5:g	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
1.02	1.07	0.28	0.15	26	1	EA:H 1:2	I-f7	1.41

^{1}H-NMR($CDCl_3$):δ 0.70(3H,d,J=6.6Hz), 0.82(3H,d,J=6.6Hz), 1.37(9H,s), 1.39(9H,s), 1.44(9H,s), 1.80-2.00(1H,m), 2.20-2.50(1H,m), 2.60-2.90(6H,m), 3.10-3.40(2H,m), 3.70-3.90(1H,m), 4.20-4.30(1H,m), 4.60-4.80(1H,m), 4.95-5.10(1H,m), 6.60(1H,d,J=7.9Hz), 6.85-7.30(6H,m)

Reaction 4

Compound I -f7:g	HCHO ml	$NaBH_3CN$ g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.75	0.48	0.14	0.13	11	1	EA:H 1:2	I-g7	0.76

^{1}H-NMR($CDCl_3$):0.83(3H,d,J=6.6Hz), 0.93(3H,d,J=6.6Hz), 1.36(9H,s), 1.41(18H,s), 1.90-3.10(10H,m), 3.10-3.30(2H,m), 3.60-3.80(1H,m), 4.40-4.60(1H,m), 4.60-4.80(1H,m), 4.90-5.05(1H,m), 6.10-6.20(1H,m), 6.30-6.40(1H,m), 6.63(1H,d,J=7.9Hz), 6.85-7.25(6H,m)

Table D-66

Example 78 (Continued from Table D-55)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Reaction 7						
Compound I-g7:g	TFA ml	CH_2Cl_2 ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.70	10	0	1	MC:M:N 100:10:1	0.46	17.7
EI-MS(M^+):486 ^{1}H-NMR($CDCl_3$):δ 0.83(3H,d,J=6.6Hz), 0.95(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.90(10H,m), 2.19(3H,s), 2.95-3.10(1H,m), 4.20-4.35(1H,m), 6.06(1H,d,J=8.3Hz), 6.62(1H,d,J=7.9Hz), 6.87(1H,dd,J=1.7,7.9Hz), 6.94-7.15(5H,m)						

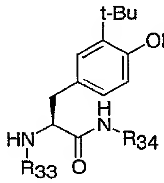
Examples 101-121 were carried out according to Scheme 3, Examples 121-131 were carried out according to Scheme 4, Example 132 was carried out according to Scheme 5, Examples 133-135 were carried out according to Scheme 6, Example 136 was carried out according to Scheme 7, Example 137 was carried out according to Scheme 8, Examples 138-165 were carried out according to Scheme 9, Examples 166 and 176 were carried out according to Scheme 10, Examples 167-171 were carried out according to Scheme 11, Examples 172 and 173 were carried out according to Scheme 12, Example 174 was carried out according to Scheme 13, Example 175 was carried out according to the scheme 14, Examples 177-179 were carried out according to Scheme 15, Example 180 was carried out according to Scheme 16, Examples 181 and 182 were carried out according to Scheme 17 and Example 183 was

carried out according to Scheme 18.

The processes of synthesizing Intermediates in Schemes 3-8 are shown below as Reference Examples. In addition, structural formulae of Intermediates of Examples 101-137 are shown in Table C-2.

Table C-2

Intermediates of Examples 101-137



T1: R33=H, R34=H

T3: R33=H, R34=Et

T6: R33=Me, R34=Et

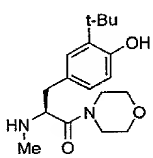
T9: R33=Et, R34=Et

T10: R33=H, R34=n-Pr

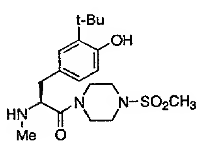
T11: R33=H, R34=i-Pr

T12: R33=Me, R34=c-Pr

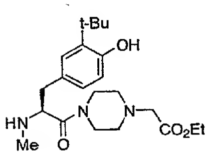
T16: R33=n-Pr, R34=H



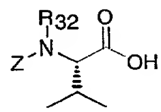
T13



T14

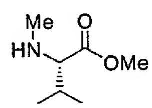


T15

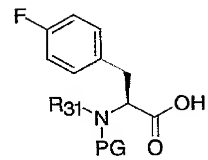


V1: R32=Me

V2: R32=Et



V3



P1: PG=Boc, R31=H

P2: PG=Boc, R31=Me

P3: PG=Z, R31=Et

P4: PG=Z, R31=H

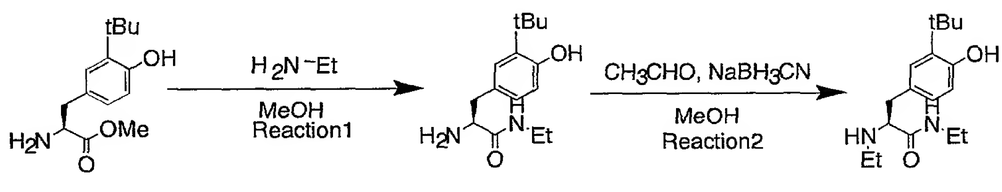
P5: PG=Z, R31=Me

Reference Example 16

Synthesis of Intermediates T3 and T9

The synthesis scheme is shown below.

Synthesis scheme of Intermediates T3 and T9



Tyr(3-tBu)-OMe T3 T9

The process of synthesizing Intermediates T3 and T9 is explained below.

Reaction step 1) Synthesis of Intermediate T3

To a solution of Tyr(3-tBu)-OMe in methanol, a 70% aqueous ethylamine solution was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T3.

Reaction step 2) Synthesis of T9

To a solution of Compound T3 and acetaldehyde in methanol, $NaBH_3CN$ was slowly added dropwise. The reaction was stopped by the addition of an aqueous $NaHCO_3$ solution and the reaction mixture was concentrated under reduced pressure. The resultant was extracted with dichloromethane,

dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T9.

The result is shown in Table E-1. In Table E-1, indications "Reaction 1" and "Reaction 2" means Reaction step 1 and Reaction step 2, "Reaction time" means stirring time, "Column sol." means the eluting solvent for silica gel column chromatography, "Product" means the obtained product and "Amount" means the yielded amount of the product. The same manner is applied to the subsequent Tables.

Table E-1

Intermediates T3 (Tyr(3-tBu)-NHEt) and T9 (N-Et-Tyr(3-tBu)-NHEt)

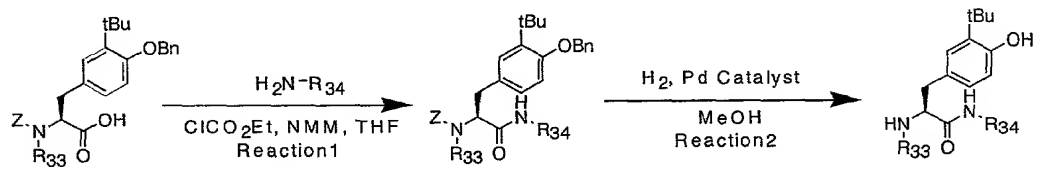
Reaction1						
Tyr(3-tBu)-OMe (g)	Ethyl amine (ml)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
14.000	168.00	56.00	18	nHx:EA=1:1	T3	12.810
Reaction2						
Compound T3(g)	CH_3CHO (ml)	$NaBH_3CN$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
12.810	2.98	3.350	100.00	0.5	MC:MeOH =20:1	8.130

Reference Example 17

Synthesis of Intermediates T6, T10, T11, T12 and T13

The synthesis scheme is shown below.

Synthesis scheme of Intermediates T6, T10, T11, T12 and T13



I-a(2)~(6) T6,10,11,12,13

R_{33} and R_{34} in the above reaction scheme indicate substituents shown in Tables E-2 to E-6.

The process of synthesizing Intermediates is explained below.

Reaction step 1)

To solutions of Z-N-Me-Tyr(O-Bn,3-tBu)-OH and ethyl chloroformate in THF, NMM was added. The mixture was stirred at room temperature and mixed with solutions of alkyl amines in THF. The mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a(2) to I-a(6).

Reaction step 2)

To solutions of Compounds I-a(2) to I-a(6) in

methanol, palladium hydroxide/carbon was added and stirred at room temperature in a hydrogen atmosphere. After filtering reaction mixtures, filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds T6, T10, T11, T12 and T13. The results are shown in Tables E-2 to E-6.

Table E-2

Intermediate T6

N-Me-Tyr(3-tBu)-NHEt

R33	R34
Me	Et

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Ethylamine (ml)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
11.300	118.80	3.40	3.90	230.00	6	nHx:EA =2:1	I-a(2)	8.400

Reaction 2

Compound I-a(2) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
6.200	0.600	120.00	3	MC:MeOH =20:1	3.600

Table E-3

Intermediate T10

Tyr(3-tBu)-NH-n-Pr

R33	R34
H	n-Pr

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	n-Propylamine (ml)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.100	1.40	0.57	0.66	30.00	2	nHx:EA:MC =1:3:1	I-a(3)	1.150

Reaction 2

Compound I-a(3) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.150	0.200	30.00	2	MC:MeOH =20:1	0.580

Table E-4

Intermediate T11

Tyr(3-tBu)-NH-i-Pr

R33	R34
H	i-Pr

Reaction1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	i-Propyl amine (ml)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	0.72	0.54	0.46	15.00	0.6	nHx:EA=2:1	I-a(4)	1.200

Reaction2

Compound I-a(4) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.200	0.500	30.00	3.5	EA:MeOH=20:1	0.660

Table E-5

Intermediate T12

N-Me-Tyr(3-tBu)-NH-c-Pr

R33	R34
Me	c-Pr

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	c-Propyl-amine (mL)	$ClCO_2Et$ (mL)	NMM (mL)	THF (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.20	0.46	0.40	30.00	2	nHx:EA:MC =1:3:1	I-a(5)	1.050

Reaction 2

Compound I-a(5) (g)	$Pd(OH)_2$ (g)	MeOH (mL)	Reaction time (hr)	Column sol.	Amount (g)
1.050	0.200	30.00	2	MC:MeOH =20:1	0.500

Intermediate P5 was synthesized according to a similar method described in Reference Example 7.

Table E-6

Intermediate T13

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-morpholin-4-ylpropan-1-one

R33	R34
Me	morpholine

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	morpholine (g)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	0.660	0.27	0.42	15.00	20	nHx:EA =1:1	I-a(6)	1.200

Reaction 2

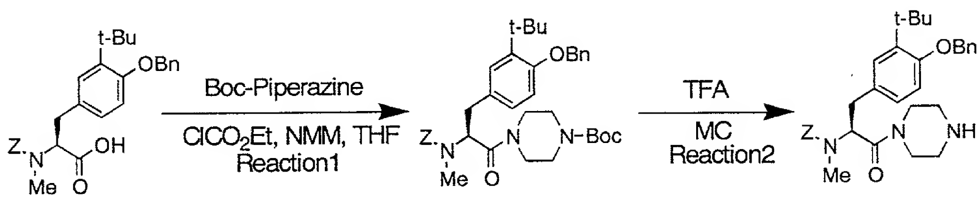
Compound I-a(6) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.200	0.300	20.00	20	MC:MeOH =20:1	0.600

Reference Example 18

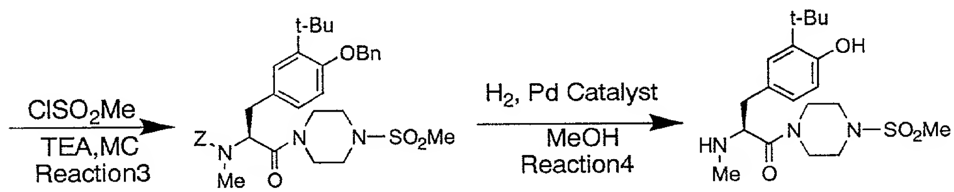
Synthesis of Intermediate T14

The synthesis scheme is shown below.

Synthesis scheme of Intermediate T14



Z-N-Me-Tyr(O-Bn, 3-tBu)-OH   I-a(7)   I-b(7)



I-c(7)   T14

The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

Compound I-a(7) was obtained according to the method described in Reaction step 1 of Reference Example 17.

Reaction step 2)

To a solution of Compound I-a(7) in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and

filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b(7).

Reaction step 3)

To a solution of Compound I-b(7) and $ClSO_2Me$ in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c(7).

Reaction step 4)

Compound T14 was obtained according to the method described in Reaction step 2 of Reference Example 17. Result is shown in Table E-7.

Table E-7

Intermediate T14

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-[4-(methylsulfonyl)piperazineyl]propane-1-one

Reaction 1

Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Boc-piperazine (g)	$ClCO_2Et$ (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	0.700	0.36	0.42	15.00	20	nHx:EA=1:1	I-a(7)	1.900

Reaction 2

Compound I-a(7) (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.900	5.00	20.00	4	MC:MeOH=20:1	I-b(7)	1.400

Reaction 3

Compound I-b(7) (g)	$ClSO_2Me$ (ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	0.46	0.82	20.00	2	MC:MeOH =20:1	I-c(7)	1.500

Reaction 4

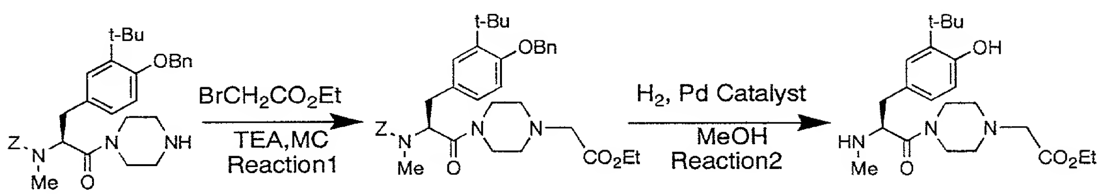
Compound I-c(7) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	0.300	20.00	20	MC:MeOH =20:1	0.900

Reference Example 19

Synthesis of Intermediate T15

The synthesis scheme is shown below.

Synthesis scheme of Intermediate T15



I-b(7) I-a(8) T15

The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

To a solution of Compound I-b(7) and ethyl 2-bromoacetate in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a(8).

Reaction step 2)

Compound T15 was obtained according to the method described in Reaction step 2 of Reference Example 17. Result is shown in Table E-8.

Table E-8

Intermediate T15

Ethyl 2-(4-{(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)propanoyl}piperazinyl)acetate

Reaction1

Compound I-b(7) (g)	Ethyl bromo acetate(ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.970	0.30	0.40	17.00	4	nHx:EA=3:1	I-a(8)	1.000

Reaction2

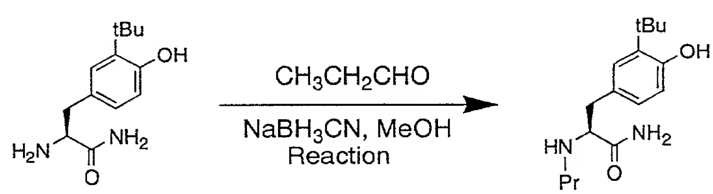
Compound I-a(8) (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Amount (g)
1.000	0.300	16.00	1	0.643

Reference Example 20

Synthesis of Intermediate T16

The synthesis scheme is shown below.

Synthesis scheme of Intermediate T16



T1 T16

The process of synthesizing Intermediate T16 is explained below.

To a solution of Compound T1 in methanol, propionaldehyde was added, stirred at room temperature for 30 min., mixed with $NaBH_3CN$ and stirred for 2 hours. The reaction mixture was mixed with a saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with

saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T16. Result is shown in Table E-9.

Table E-9

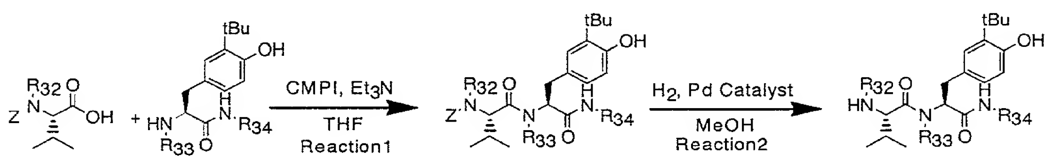
Intermediate T16

N-Pr-Tyr(3-tBu)-NH_2

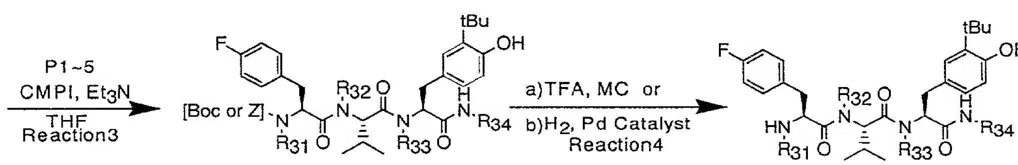
Reaction						
Compound T1 (g)	CH_3CH_2CHO (ml)	$NaBH_3CN$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	1.34	1.170	70.00	2	nHx:EA=1:2	1.580

Scheme 3 shows the synthesis process of Examples 101-121.

Scheme 3: Synthesis process of Examples 101-121



V1,2 T3,6,9,10-15 I-a101-121 I-b101-121



I-c101-121

R_{31}, R_{32}, R_{33} and R_{34} in the above reaction scheme

indicate substituents shown in Tables D-101 to D-121.

The synthesis process in scheme 3 is explained below.

Reaction step 1)

To solutions of Compounds T, Compounds V and CMPI in THF, TEA was added under cooling and stirred at room temperature. The mixtures were mixed with water, extracted with ethyl acetate, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a101 to I-a121.

Reaction step 2)

To solutions of Compounds I-a101 to I-a121 in methanol, Pd/C was added and stirred at room temperature in a hydrogen atmosphere. After filtering off the Pd/C, the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-b101 to I-b121.

Reaction step 3)

To solutions of Compounds I-b101 to I-b121, P1 to P5 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-c101 to I-c121.

Reaction step 4-a)

To solutions of Compounds I-c101 to I-c121 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were neutralized by the addition of a saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving the titled compounds.

Reaction step 4-b)

To solutions of Compounds I-c101 to I-c121 in methanol, Pd/C or $Pd(OH)_2$ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C or $Pd(OH)_2$, the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 3 are shown in Tables D-101 to D-121.

Table D-101

Example 101

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
H	Me	H	Et

Reaction1

Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a101	5.220

Reaction2

Compound I-a101(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.500	0.450	45.00	20	MC:MeOH =20:1	I-b101	2.200

Reaction3

Compound I-b101(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.500	0.600	0.50	15.00	20	nHx:EA =1:1	I-c101	0.830

Reaction4-b

Compound I-c101(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.830	0.100	10.00	20	MC:MeOH =10:1	0.170	18.42

ESI-MS(M^++1): 557

1H-NMR($CDCl_3$): δ 0.59-1.05(9H,m), 1.37(9H, s), 2.25-2.39(1H, m), 2.58-3.24(9H, m),3.58-3.97(2H,m), 4.44-4.62(1H,m), 5.59-5.77(1H,m), 6.60-7.72(8H,m), 9.03 and 9.06(1H, d, J=7.9Hz)

Table D-102

Example 102

N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Me	Me	H	Et

Reaction1

Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a102	5.220

Reaction2

Compound I-a102(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.500	0.450	45.00	20	MC:MeOH =20:1	I-b102	2.200

Reaction3

Compound I-b102(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.000	1.310	0.72	20.00	20	nHx:EA =1:1	I-c102	1.560

Reaction4-a

Compound I-c102(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.500	1.70	10.00	4	MC:MeOH =10:1	0.28	18.73

ESI-MS(M^++1): 557

1H-NMR($CDCl_3$): (two rotamers) δ 0.57, 0.79, 0.92 and 1.00(9H, d and m, J=6.3-6.8Hz), 1.34and 1.38(9H, s), 2.25, 2.40 and 2.58, 2.65(6H, s), 2.05-2.40(1H, m), 2.67-3.25(6H, m), 3.55 nad 3.68(1H,m), 3.84, 4.40 and 4.55(2H, d and m, J=10.9Hz), 5.56 and 5.72(1H,m), 6.65-7.17(8H,m), 9.15 and 9.18 (1H, d, J=8.2Hz)

Table D-103

Example 103

N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Et	Me	H	Et

Reaction1

Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a103	5.220

Reaction2

Compound I-a103(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.500	0.450	45.00	20	MC:MeOH =20:1	I-b103	2.200

Reaction3

Compound I-b103(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.670	1.050	0.57	20.00	20	nHx:EA =1:1	I-c103	0.800

Reaction4-b

Compound I-c103(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.800	0.100	10.00	20	MC:MeOH =10:1	0.220	19.27

ESI-MS(M^++1): 571

1H-NMR($CDCl_3$): (two rotamers) δ 0.42-1.20(12H,m), 1.35 and 1.39(9H, s), 2.05-2.26(1H, m), 2.31-2.54(1H, m),2.40 and 2.50(3H,s), 2.62-3.26(6H,m), 3.62-3.80(1H,m),4.34-4.58(1H,m), 5.79-5.87(1H, m), 6.60-7.04(7H, m)

Table D-104

Example 104

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt

R31		R32		R33		R34		
H		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a104	4.200
Reaction2								
Compound I-a104 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH =20:1		I-b104	3.900	
Reaction3								
Compound I-b104(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.600	1.300	0.90	30.00	18	nHx:EA =1:2	I-c104	0.920
Reaction4-b								
Compound I-c104(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.920	0.100	10.00	3	MC:MeOH =20:1		0.210	19.57	
ESI-MS(M^++1): 557								
1H-NMR($CDCl_3$): (two rotamers) δ 0.56, 0.77, 0.79 and 0.92(6H, d, J=6.4-6.7Hz), 1.01-1.12(3H, m), 1.38 and 1.33(9H, s), 2.19-2.68(2H, m), 2.52 and 2.83(3H, s), 2.68-3.42(4H, m), 3.00 and 3.02(3H, s),3.65-3.87(1H, m), 4.90-5.11 and 5.35-5.47(2H, m), 5.95-6.08(1H, m), 6.36 and 6.62(1H, d, J=7.8-7.9Hz), 6.68-7.16(6H, m)								

Table D-105

Example 105

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Me	Me	Me	Et

Reaction1

Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a105	4.200

Reaction2

Compound I-a105 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.200	0.400	75.00	5	MC:MeOH =20:1	I-b105	3.900

Reaction3

Compound I-b105 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.480	1.300	0.90	30.00	18	nHx:EA =1:2	I-c105	1.020

Reaction4-a

Compound I-c105 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.020	2.30	23.00	6	MC:MeOH =20:1	0.200	20.213

ESI-MS(M^++1): 571

1H-NMR($CDCl_3$): (two rotamers) δ 0.63, 0.80, 0.81 and 0.92(6H, d, J=6.4-6.9Hz), 1.06(3H, t, J=7.3Hz), 1.34 and 1.39(9H, s), 2.13-2.33(1H, m), 2.22 and 2.25(3H, s), 2.53 and 2.82(3H s), 2.54(1H, s), 2.60-2.70(2H, m), 2.74-2.90(1H, m), 2.95 and 3.06(3H, s),3.45 and 3.59(1H, t, J=5-6.8Hz),5.07 and 5.15(1H, d, J=10.6-10.9Hz), 5.05 and 5.38(1H, dd, J=8.1-9.3, 6.1-6.8Hz), 6.0(1H, t, J=5.0Hz),6.40 and 6.61(1H, d, J=8.0Hz), 6.75(3H, m), 7.02-7.18(3H, m)

Table D-106

Example 106

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Et	Me	Me	Et

Reaction1

Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a106	4.200

Reaction2

Compound I-a106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.200	0.400	75.00	5	MC:MeOH= 20:1	I-b106	3.900

Reaction3

Compound I-b106 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.740	1.300	0.90	30.00	15	nHx:EA =1:2	I-c106	1.050

Reaction4-b

Compound I-c106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.050	0.100	14.00	3	MC:MeOH= 20:1	0.200	20.950

ESI-MS(M^++1): 585

1H-NMR($CDCl_3$): (two rotamers) δ 0.65, 0.79, 0.8 and 0.91(6H, d, J=6.0Hz), 0.97-1.08(6H, m),1.34 and 1.39(9H, s), 2.21-2.38(2H, m), 2.46-2.59(2H, m), 2.61-2.9(2H, m),2.5 and 2.75(3H, s),2.96 and 3.06(3H, s), 3.17-3.46(2H, m), 3.55 and 3.68(1H, t, J=7.0Hz), 5.01-5.36(2H, m), 5.97-6.0(1H, m), 6.41 and 6.59(1H, d, J=8.0Hz), 6.79-6.98(3H, m), 7.04-7.17(3H, m)

Table D-107

Example 107

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt

R31		R32		R33		R34		
H		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a107	3.030
Reaction2								
Compound I-a107(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15	MC:MeOH = 10:1		I-b107	5.000	
Reaction3								
Compound I-b107(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.815	0.606	0.40	30.00	18	nHx:EA=1:2	I-c107	1.040
Reaction4-b								
Compound I-c107(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.047	0.156	20.00	3.5	MC:MeOH =20:1		0.252	21.09	
ESI-MS(M^++1):571								
1H-NMR($CDCl_3$):(two rotamers) δ 0.74, 0.80 and 0.92(6H, d, J=7.0-7.9Hz), 0.97-1.20(6H, m),1.32 and 1.36(9H, s), 2.20-3.13(5H, m), 2.74 and 3.05(3H, s), 3.15-3.35(3H, m), 3.35-3.95(3H, m), 4.92-5.10(2H, m), 6.44 and 6.73(1H, d, J=8.8Hz), 6.50(3/5H, m), 6.75(3/5H, dd, J=7.9, 1.7Hz), 6.90-7.29(29/5H, m)								

Table D-108

Example 108

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt

R31		R32		R33		R34		
Me		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a108	3.030
Reaction2								
Compound I-a108(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15.00	MC:MeOH = 10:1		I-b108	5.000	
Reaction3								
Compound I-b108(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.022	1.130	0.966	0.70	20.00	19	nHx:EA=1:2	I-c108	1.590
Reaction4-a								
Compound I-c108(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.590	1.80	10.00	3	MC:MeOH =20:1		0.251	21.54	
ESI-MS(M^++1):585								
1H-NMR($CDCl_3$):(two rotamers) δ 0.78-0.90 and 0.95(6H, m and d, J=7.9Hz), 0.97-1.10(3H, m), 1.10 and 1.22(3H, m),1.31 and 1.39(9H, s), 2.21-2.25(3H, s), 2.19-2.40(1H, m),2.55-3.35(7H, m), 2.69 and 2.72(3H, s), 3.42-3.75(3H, m),4.95-5.10(1H, m),5.12(1H, d, J=10.6Hz),6.44 and 6.58(1H, d, J=8.8Hz), 6.50(3/5H,m), 6.79(3/5H, dd, J=8.1, 2.5Hz), 6.88-7.00(12/5H, m), 7.05-7.20(12/5H, m) 7.27(1H, brs)								

Table D-109

Example 109

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Et	Me	Et	Et

Reaction1

Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a109	3.030

Reaction2

Compound I-a109(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
8.000	1.200	50.00	15	MC:MeOH = 10:1	I-b109	5.000

Reaction3

Compound I-b109(g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.819	0.606	0.40	16.00	18	nHx:EA=1:2	I-c109	1.000

Reaction4-b

Compound I-c109(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.000	0.150	20.00	15	MC:MeOH =20:1	0.127	21.920

ESI-MS(M^++1):599

1H-NMR($CDCl_3$):(two rotamers) δ 0.78-0.88 and 0.92(6H, m and d, J=7.4Hz), 0.98-1.18(6H, m), 1.20(3H, q, J=6.4Hz), 1.34 and 1.38(9H, s), 2.20-2.43(2H, m),2.43-3.35(8H, m),2.68 and 2.80(3H, s), 3.42-3.78(3H, m), 4.90-5.12(1H, m), 5.12(1H, d, J=10.6Hz), 6.42 and 6.58(1H, d, J=15.3Hz), 6.50(1/3H,m), 6.80(2/3H, dd, J=8.8, 2.1Hz), 6.85-7.00(3H, m),7.05-7.17(10/3H, m),7.30(2/3H, brs)

Table D-110

Example 110

Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHEt

<table>
<tr><td colspan="2">R31</td><td colspan="2">R32</td><td colspan="2">R33</td><td colspan="3">R34</td></tr>
<tr><td colspan="2">H</td><td colspan="2">Et</td><td colspan="2">H</td><td colspan="3">Et</td></tr>
<tr><td colspan="9">Reaction1</td></tr>
<tr><td>Compound T3 (g)</td><td>Compound V2 (g)</td><td>CMPI (g)</td><td>TEA (ml)</td><td>THF (ml)</td><td>Reaction time (hr)</td><td>Column sol.</td><td>Product</td><td>Amount (g)</td></tr>
<tr><td>6.000</td><td>6.240</td><td>8.700</td><td>6.60</td><td>120.00</td><td>20</td><td>nHx:EA=1:1</td><td>I-a110</td><td>9.540</td></tr>
<tr><td colspan="9">Reaction2</td></tr>
<tr><td>Compound I-a110 (g)</td><td>Pd(OH)$_2$ (g)</td><td>MeOH (ml)</td><td>Reaction time (hr)</td><td colspan="2">Column sol.</td><td>Product</td><td colspan="2">Amount (g)</td></tr>
<tr><td>6.000</td><td>0.600</td><td>60.00</td><td>20</td><td colspan="2">MC:MeOH =20:1</td><td>I-b110</td><td colspan="2">3.570</td></tr>
<tr><td colspan="9">Reaction3</td></tr>
<tr><td>Compound I-b110(g)</td><td>Compound P1 (g)</td><td>CMPI (g)</td><td>TEA (ml)</td><td>THF (ml)</td><td>Reaction time (hr)</td><td>Column sol.</td><td>Product</td><td>Amount (g)</td></tr>
<tr><td>1.200</td><td>1.500</td><td>2.000</td><td>1.00</td><td>20.00</td><td>20</td><td>nHx:EA =1:1</td><td>I-c110</td><td>0.400</td></tr>
<tr><td colspan="9">Reaction4-a</td></tr>
<tr><td>Compound I-c110(g)</td><td>TFA (ml)</td><td>MC (ml)</td><td>Reaction time (hr)</td><td colspan="2">Column sol.</td><td>Amount (g)</td><td colspan="2">HPLC min</td></tr>
<tr><td>0.400</td><td>0.60</td><td>3.00</td><td>4</td><td colspan="2">MC:MeOH =20:1</td><td>0.200</td><td colspan="2">20.25</td></tr>
<tr><td colspan="9">ESI-MS(M$^+$+1): 557</td></tr>
<tr><td colspan="9">1H-NMR(CDCl$_3$): δ 0.62-1.16(12H,m), 1.38(9H, s), 2.25-2.45(1H, m), 2.62-3.86(9H, m),3.92 and 3.95(1H, d, J=10.0Hz), 4.44-5.56(1H, m), 5.67-5.90(1H, m), 6.60-7.20(7H, m),9.05 and 9.08(1H, d, J=7.8Hz)</td></tr>
</table>

Table D-111

Example 111

N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Me	Et	H	Et

Reaction1

Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a111	9.540

Reaction2

Compound I-a111 (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	0.600	60.00	20	MC:MeOH =20:1	I-b111	3.570

Reaction3

Compound I-b111(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.600	2.000	1.00	20.00	20	nHx:EA =1:1	I-c111	0.400

Reaction4-a

Compound I-c111(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.400	0.60	3.00	4	MC:MeOH =20:1	0.300	20.77

ESI-MS(M^++1): 571

1H-NMR($CDCl_3$): (two rotamers) δ 0.67 and 0.80-1.16(12H, d and m, J=6.8Hz), 1.37(9H, s), 2.30(3H, s), 2.35-2.39(1H, m), 2.79-3.22(8H, m), 3.53-3.59(1H, m), 4.04-4.15(1H, m), 4.39-4.46(1H, m), 5.73-5.77(1H, m), 6.61 and 6.64(1H, d, J=8.2Hz), 6.84-7.19(6H, m)

Table D-112

Example 112

N-Et -Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Et	Et	H	Et

Reaction1

Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a112	9.540

Reaction2

Compound I-a112 (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.200	0.600	60.00	20	MC:MeOH =20:1	I-b112	3.570

Reaction3

Compound I-b112(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.585	2.000	1.00	20.00	20	nHx:EA =1:1	I-c112	0.550

Reaction4-b

Compound I-c112(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.400	0.050	4.00	20	MC:MeOH =30:1	0.098	21.090

ESI-MS(M^++1): 585

1H-NMR($CDCl_3$): (two rotamers) δ 0.48 and 0.71-1.31(15H, d and m, J=7.4Hz), 1.37(9H, s), 2.20-2.61(2H, m), 2.71-3.34(10H, m), 3.60-3.82(2H, m), 4.40-4.56(1H, m), 5.80-5.98(1H, m), 6.67-7.01(3H, m), 7.02-7.16(3H, m), 7.48 and 7.50(1H, d, J=6.8Hz), 8.73 and 8.76(1H,d, J=7.9Hz)

Table D-113

Example 113

Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
H	Et	Me	Et

Reaction1

Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a113	5.500

Reaction2

Compound I-a113 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.500	0.500	100.00	2	MC:MeOH =20:1	I-b113	3.200

Reaction3

Compound I-b113 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c113	0.320

Reaction4-a

Compound I-c113 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.320	0.70	7.40	6	MC:MeOH =20:1	0.020	20.260

ESI-MS(M^{+}+1): 571

1H-NMR($CDCl_3$): (two rotamers) δ 0.36-0.96(8H,m), 0.98-1.10(4H,m), 1.35 and 1.39(9H,s), 2.28-2.41(1H,m), 2.84 and 3.04(3H,s), 2.55-3.39(8H,m), 3.68-3.78(1H,m), 4.90-5.32(2H,m) 6.45 and 6.65(1H, d, J=6.0Hz),6.77-7.23(6H,m)

Table D-114

Example 114

N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Me	Et	Me	Et

Reaction1

CompoundT6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a114	5.500

Reaction2

Compound I-a114 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.500	0.500	100.00	2	MC:MeOH =20:1	I-b114	3.200

Reaction3

Compound I-b114 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	20	nHx:EA =1:2	I-c114	0.300

Reaction4-a

Compound I-c114 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.300	0.70	6.80	6	MC:MeOH =20:1	0.030	20.880

ESI-MS(M$^+$+1): 585

1H-NMR($CDCl_3$): (two rotamers) δ 0.51, 0.81, 0.87 and 0.91(6H, d, J=6.3-6.9Hz), 0.94, 1.04 and 1.17(6H, t, J=3.6Hz), 1.34 and 1.39(9H,s), 2.18-2.62(1H, m), 2.38(3H, s), 2.57-2.88 (3H,m), 2.91-3.38(5H,m), 2.94 and 3.06(3H,s), 3.49 and 3.57(1H, t, J=6.4-7.2Hz), 5.49-5.32 (2H,m), 6.02-6.1 and 6.53-6.59(1H, m), 6.45 and 6.64(1H, d, J=8.0Hz),6.76-7.03(3H, m),7.08 -7.19(3H, m)

Table D-115

Example 115

N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NHEt

R31	R32	R33	R34
Et	Et	Me	Et

Reaction1

Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a115	5.500

Reaction2

Compound I-a115 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.500	0.500	100.00	2	MC:MeOH =20:1	I-b115	3.200

Reaction3

Compound I-b115 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c115	0.300

Reaction4-b

Compound (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.300	0.030	4.00	3	MC:MeOH =20:1	0.040	21.59

ESI-MS(M^++1): 599

1H-NMR($CDCl_3$):(two rotamers) δ 0.38-1.17(15H,m), 1.34, 1.36 and 1.38(9H,s), 3.38-2.12 (1H,m), 3.55(1H, t, J=6.3Hz), 3.47-3.72(1H, m), 4.88-5.37(2H, m), 5.79-6.09 and 6.63-6.7(1H, m), 6.42 and 6.62(1H, dd, J=8.3,7.4Hz), 7.05-7.22(6H,m)

Table D-116

Example 116

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt

R31		R32		R33		R34		
H		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a116	3.030
Reaction2								
Compound I-a116(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	MC:MeOH =10:1		I-b116	2.24	
Reaction3								
Compound I-b116(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.680	0.549	0.40	12.00	18	nHx:EA=1:1	I-c116	0.200
Reaction4-b								
Compound I-c116(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.200	0.030	4.00	3	MC:MeOH =20:1		0.053	21.59	
ESI-MS(M^++1):585								
1H-NMR($CDCl_3$):(two rotamers) δ 0.60 and 0.78-1.30(15H, d and m, J=7.9Hz), 1.34 and 1.38(9H, s), 2.22-2.50(1H, m), 2.52-3.00(3H, m), 3.00-3.54(6H, m), 3.54-3.94(2H, m), 4.82-5.05(1H, m), 5.10(1H, m), 6.45-6.70(2H, m), 6.80(3/4H, m), 6.91-7.25(21/4H, m)								

Table D-117

Example 117

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt

R1	R2	R3	R4
Me	Et	Et	Et

Reaction1

Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a117	3.030

Reaction2

Compound I-a117(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.030	0.454	60.00	14	MC:MeOH = 10:1	I-b117	2.240

Reaction3

Compound I-b117(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.845	0.681	0.585	0.40	16.00	48	nHx:EA=1:1	I-c117	0.378

Reaction4-a

Compound I-c117(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.378	0.80	4.00	3	MC:MeOH =20:1	0.056	22.20

ESI-MS(M^++1):599

1H-NMR($CDCl_3$):(two rotamers) δ 0.75 and 0.83-1.10(10H, d and m, J=7.9Hz), 1.10-1.30(5H, m), 1.35 and 1.39(9H, s), 2.30 and 2.33(3H, s), 2.30-2.48(1H, m), 2.65-3.89(12H, m), 4.90 and 5.07(1H, m), 5.18 and 5.23(1H, d, J=9.7Hz), 6.48 and 6.58(1H, d, J=8.8Hz), 6.63(1/2H, m), 6.80(1H, dd, J= 8.1, 1.8Hz), 6.90-7.0(7/2H, m), 7.05(1/2H, d, J=1.7Hz), 7.06-7.20(5/2H, m)

Table D-118

Example 118

N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHEt

R31		R32		R33		R34		
Et		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.0	16	nHx:EA=3:1	I-a118	3.030
Reaction2								
Compound I-a118(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	MC:MeOH =10:1		I-b118	2.240	
Reaction3								
Compound I-b118(g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.520	0.642	0.475	0.30	10.00	48	nHx:EA=1:1	I-c118	0.174
Reaction4-b								
Compound I-c118(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.174	0.026	4.00	3	MC:MeOH =20:1		0.141	22.84	
ESI-MS(M^++1):613								
1H-NMR($CDCl_3$):(two rotamers) δ 0.75 and 0.80-0.98(8H, d and m, J=7.9Hz), 0.98-1.08(6H, m),1.08-1.23(4H, m), 1.34 and1.38(9H, s), 2.23-2.88(6H, m), 2.93-3.88(9H, m), 4.92 and 5.08(1H, m), 5.15 and 5.22(1H, d, J=9.7Hz), 6.49 and 6.57(1H, d, J=8.8Hz), 6.63(1/2H, m), 6.80(1/2H, dd, J=8.1, 1.7Hz), 6.85-7.00(3H, m), 7.05(1/2H, d, J=1.7Hz), 7.08-7.20(5/2H, m)								

Table D-119

Example 119

Phe(4-F)-N-Me-Val-Tyr(3-t Bu)-NH-n-Pr

R31	R32	R33	R34
H	Me	H	n-Pr

Reaction1

Compound T10(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.580	0.640	0.670	0.92	10.00	18	nHx:EA=1:1	I-a119	1.030

Reaction2

Compound I-a119(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.030	0.200	10.00	2	MC:MeOH =15:1	I-b119	0.76

Reaction3

Compound I-b119(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	0.660	0.650	1.07	10.00	19	nHx:EA=1:2	I-c119	1.100

Reaction4-a

Compound I-c119(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.100	6.66	13.30	2	MC:MeOH =15:1	0.210	20.10

ESI-MS(M^{+}+1):557

1H-NMR($CDCl_3$): (two rotamers) δ 0.68-0.92(9H, m), 1.38 and 1.39(9H, s), 2.69 and 2.85 (3H, s), 1.37-3.20(7H, m), 3.62-3.90(1H, m), 3.93(1H, d, J=10.9Hz), 4.42-4.57(1H, m), 6.62-7.17(7H, m)

Table D-120

Example 120

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr

R31	R32	R33	R34
H	Me	H	i-Pr

Reaction1

Compound T11 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.630	0.910	0.66	10.00	3	nHx:EA= 1:1	I-a120	1.210

Reaction2

Compound I-a120 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.210	0.500	20.00	2	MC:MeOH =20:1	I-b120	0.900

Reaction3

Compound I-b120 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.900	0.650	0.880	0.64	15.00	3	nHx:EA =2:1	I-c120	1.300

Reaction4-a

Compound I-c120 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.300	5.00	20.00	2	MC:MeOH = 25:1	0.960	19.99

ESI-MS(M^++1):557

1H-NMR($CDCl_3$) : (two rotamers) δ 0.70-1.07(12H, m), 1.35 and 1.38(9H, s), 1.72(2H, brs), 2.29-2.37(1H, m), 2.72 and 2.83(3H, s), 2.52-2.74(4H, m), 3.60 and 3.81(1H, dd, J=8.2 , 3.0Hz), 3.85-3.98(2H, m), 4.42-4.60(1H, m), 5.48 and 5.69(1H, d, J=7.8Hz), 6.62-6.80(2H, m), 6.90-6.98(3H, m), 7.06-7.11(2H, m), 9.07(1H, d, J=8.2Hz)

Table D-121

Example 121

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr

R31	R32	R33	R34
H	Me	Me	c-Pr

Reaction1

Compound T12(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.520	0.600	0.70	10.00	18	nHx:EA:MC =1:1:1	I-a121	0.850

Reaction2

Compound I-a121(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.850	0.200	10.00	2	MC:MeOH=15:1	I-b121	0.400

Reaction3

Compound I-b121(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.540	0.550	0.57	10.00	19	nHx:EA:MC =1:3:1	I-c121	0.720

Reaction4-a

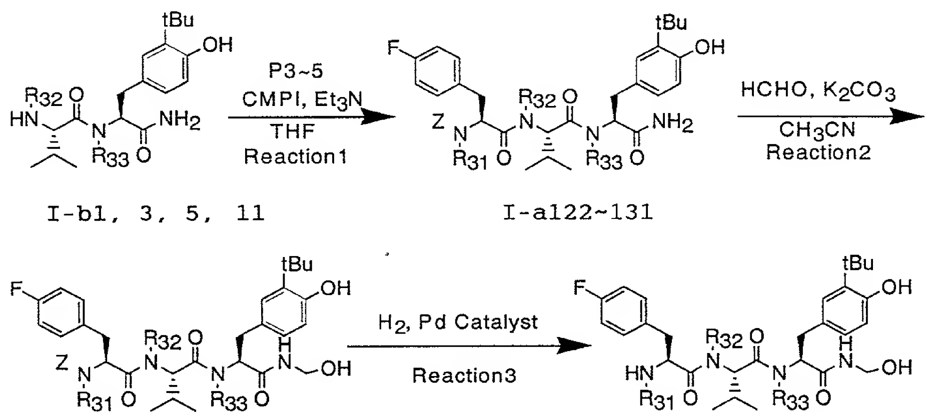
Compound I-c121(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.700	3.30	6.60	2	MC:MeOH =15:1	0.210	18.12

ESI-MS(M^++1):569

1H-NMR($CDCl_3$): (two rotamers) δ 0.17-0.88(11H, m), 1.31 and 1.34(9H, s), 2.28, 2.63, 2.90 and 3.93(6H, s), 2.11-3.08 (6H, m), 4.43-5.26(3H, m), 6.48 and 6.61(1H, d, J=7.9Hz), 6.62-7.16(6H, m)

Scheme 4 shows the synthesis process of Examples 122-131

Scheme 4: Synthesis process of Examples 122-131



I-b1, 3, 5, 11

I-a122~131

I-b122~131

R_{31}, R_{32}, and R_{33} in the above reaction scheme indicate substituents shown in Tables D-122 to D-131.

The synthesis process in scheme 4 is explained below.

Reaction step 1)

To solutions of Compounds I-b1, I-b3, I-b5 and I-b11, Compounds P3 to P5 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a122 to I-a131.

Reaction step 2)

To solutions of Compounds I-a122 to I-a131 in CH_3CN, 38% HCHO and an aqueous K_2CO_3 solution were added and stirred at room temperature. The reaction mixtures were mixed with a saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compounds I-b122 to I-b131.

Reaction step 3)

To solutions of Compounds I-b122 to I-b131 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C, the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 4 are shown in Tables D-122 to D-131.

Table D-122

Example 122

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
H	Me	H

Reaction1

Compound I-b1 (g)	CompoundP4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.760	0.610	0.56	40.00	4	nHx:EA=2:1	I-a122	1.000

Reaction2

Compound I-a122(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.15	0.430	30.00	2	nHx:EA:MC =1:3:1	I-b122	0.900

Reaction3

Compound I-b122(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.900	0.140	13.00	2	EA:MeOH=15:1	0.560	15.91

ESI-MS(M^++1):545

1H-NMR($CDCl_3$):(two rotamers) δ 0.69, 0.75, 0.83 and 0.90(6H, d, J=6.4-6.7Hz), 1.34 and 1.35(9H, s), 2.22-3.17(5H, m) 2.68 and 2.88(3H, s), 3.57 and 3.82(1H, dd, J=8.0-8.5, 5.5-6.0Hz), 4.51-4.74(3H, m), 6.61-9.02(8H, m)

Table D-123

Example 123

N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$

R31			R32			R33		
Me			Me			H		
Reaction1								
Compund I-b1 (g)	Compound P5(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.569	0.439	0.60	20.00	16	nHx:EA=1:1	I-a123	0.920
Reaction2								
Compound I-a123(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.910	1.00	0.380	25.00	2	nHx:EA=1:1	I-b123	0.927	
Reaction3								
Compound I-b123(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.270	0.100	10.00	1.5	EA:MeOH=30:1		0.228	16.04	
ESI-MS(M^++1):559								
1H-NMR($CDCl_3$):(two rotamers) δ 0.52, 0.77 and 0.89(6H, d, J=6.5-6.8Hz), 1.31 and 1.37(9H, s), 2.08-2.17(1H, m), 2.24 and 2.28(3H, s), 2.46 and 2.56(3H, s), 2.58-3.06(4H, m), 3.54-4.35(2H, m), 6.62-7.34(7H, m)								

Table D-124

Example 124

N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Et	Me	H

Reaction1

Compund I-b1 (g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.750	0.555	0.75	20.00	26	nHx:EA=1:1	I-a124	0.987

Reaction2

Compound I-a124(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.980	1.10	0.400	25.00	2	nHx:EA=1:1	I-b124	0.911

Reaction3

Compound I-b124(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.910	0.200	15.00	3	MC:MeOH=15:1	0.250	16.36

ESI-MS(M^++1):573

1H-NMR($CDCl_3$):(two rotamers) δ 0.50, 0.75, 0.82 and 0.85(6H, d, J=6.3-7.0Hz), 0.98 and 1.12(3H, t, J=6.7Hz), 1.40 and 1.45(9H, s), 2.15(1H, m), 2.42 and 2.46(3H, s),2.40(2H, m), 2.60-3.10(5H, m),3.63(1H, dd, J=10.6, 6.0Hz), 4.50(1H, m), 4.70(2H, m), 6.70(4H, m), 6.90(1H, m), 7.00(1H, s), 7.12(1H, s), 7.20 and 7.40(1H, m), 8.75(1H, d, J=6.6Hz)

Table D-125

Example 125

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Me	Me	Me

Reaction 1

Compound I-b3(g)	Compound P5 (g)	CMPI (g)	TEA (mL)	THF (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	1.420	1.100	0.92	30.00	14	nHx:EA:MC =1:2:1	I-a125	1.800

Reaction 2

Compound I-a125(g)	HCHO (mL)	K_2CO_3 (g)	CH_3CN (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.790	1.970	0.730	52.00	2	nHx:EA:MC =1:3:1	I-b125	1.500

Reaction 3

Compound I-b125(g)	Pd/C (g)	MeOH (mL)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.500	0.230	20.00	2	EA:MeOH=10:1	0.970	17.27

ESI-MS(M^++1):573

1H-NMR($CDCl_3$):(two rotamers) d 0.57, 0.79 and 0.92(6H, d, J=6.3-6.8Hz), 1.34 and 1.38(9H, s), 2.22 and 2.25(3H, s) 2.29(1H, m), 2.52 and 2.82(3H, s), 2.55-2.89(3H, m), 2.92 and 3.04(3H, s), 3.20 and 3.39(1H, dd, J=11.1-14.1,6.3-7.3Hz), 3.46 and 3.61(1H, t, J=6.8-6.9Hz), 4.59-4.76(2H, m), 5.03 and 5.14(1H, d, J=10.5Hz), 5.11 and 5.37(1H, dd, J=6.3, 9.73Hz), 6.39 and 6.61(1H,d,J=7.9-8.2Hz),6.77-7.12(6H,m)

Table D-126

Example 126

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Et	Me	Me

Reaction1

Compund I-b3(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	1.720	1.270	1.07	38.00	14	nHx:EA =2:1	I-a126	2.110

Reaction2

Compound I-a126(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.050	2.20	0.820	59.00	2	nHx:EA:MC =1:3:1	I-b126	2.000

Reaction3

Compound I-b126(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.950	0.290	27.00	2	EA:MeOH =10:1	1.350	18.09

ESI-MS(M^++1):587

1H-NMR($CDCl_3$):(two rotamers) δ 0.60, 0.79 and 0.91(6H, d, J=6.4-6.5Hz), 1.00 and 1.04(t, 3H, J=6.7-7.2Hz), 1.34 and 1.39(9H, s), 2.18-2.89(7H, m) 2.52 and 2.77(3H, s), 2.95 and 3.04(3H, s), 3.22 and 3.39(1H, dd, J=14.0-15.0, 7.9-7.6Hz),3.57 and 3.70(t, 1H, J=6.8, 6.9Hz), 4.59-4.73(2H, m),5.05 and 5.13(1H, d, J=10.6-10.7Hz), 5.13 and 5.31(1H, dd, J=9.0,7.3Hz), 6.45 and 6.62(1H, d, J=7.9 and 8.04Hz), 6.78-7.12(6H, m)

Table D-127

Example 127

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$

R31			R32			R33		
H			Me			Et		
Reaction1								
Compund I-b5 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.240	0.990	0.91	20.00	12	nHx:EA=1:1	I-a127	0.440
Reaction2								
Compound I-a127(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.420	0.76	0.035	5.00	12	nHx:EA=1:1	I-b127	0.370	
Reaction3								
Compound I-b127(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	0.050	15.00	3	MC:MeOH=20:1		0.100	18.26	
ESI-MS(M^++1):573								
1H-NMR($CDCl_3$) : (two rotamers) δ 0.67, 0.81 and 0.91(6H, d, J=5.9-6.9Hz),1.07 and 1.16(3H, t, J=6.8 and 6.1Hz), 1.33 and 1.38(9H, s), 2.24-2.49(2H, m) 2.58-2.75(1H, m), 2.78 and 3.05(3H, s),2.83-3.03(1H, m), 3.15-3.30(1H, m), 3.37-3.44(1H, m), 3.55-3.65(1H, m), 3.75-3.90(1H, m), 4.55-4.76(2H, m),4.85-5.06(2H, m), 6.43 and 6.61(1H, d, J=8.1-8.4Hz), 6.75-7.1(6H, m), 7.36 and 8.03(1H, brs)								

Table D-128

Example 128

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Me	Me	Et

Reaction1

Compund I-b5(g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.230	0.950	0.91	20.00	12	nHx:EA =1:1	I-a128	0.640

Reaction2

Compound I-a128(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.610	1.10	0.051	3.00	12	nHx:EA =1:1	I-b128	0.560

Reaction3

Compound I-b128(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.540	0.080	23.00	1	MC:MeOH=20:1	0.200	18.85

ESI-MS(M^++1):587

1H-NMR($CDCl_3$):(two rotamers) δ 0.77, 0.83, 0.84 and 0.93(6H, d, J=6.4-6.8Hz),1.12 and 1.18(3H, t, J=7.0-7.1Hz), 1.34 and 1.38(9H, s), 2.25(3H, s), 2.29-2.39(1H, m), 2.64-3.01(3H, m), 2.75 and 2.85(3H, s), 3.21-3.33(1H, m), 3.42-3.69(3H, m), 4.58-4.76(2H, m), 4.88-4.94 and 5.10-5.19(1H, m), 5.12(1H, dd, J=10.5, 2.6Hz), 6.50 and 6.61(1H, d, J=8.0Hz), 6.80-6.98(3H, m), 7.07-7.15(3H, m), 7.42 and 8.29(1H, t, J=6.0-6.4Hz)

Table D-129

Example 129

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Et	Me	Et

Reaction1

Compund I-b5 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.370	1.010	0.92	25.00	12	nHx:EA =1:1	I-a129	0.970

Reaction2

Compound I-a129(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.950	1.70	0.079	6.00	12	nHx:EA =1:1	I-b129	0.790

Reaction3

Compound I-b129(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.780	0.120	30.00	2	MC:MeOH =20:1	0.300	19.68

ESI-MS(M^++1):601

1H-NMR($CDCl_3$):(two rotamers) δ 0.76, 0.82, 0.83 and 0.92(6H, d, J=6.4-6.9Hz), 1.00-1.28(6H, m), 1.34 and 1.38(9H,s), 2.25-2.43(2H, m), 2.49-2.59(1H, m), 2.65-2.97(3H, m), 2.72 and 2.79(3H, s), 3.17-3.33(1H, m), 3.41-3.76(3H, m), 4.52-4.74(2H, m), 4.85-4.90 and 5.12-5.16(1H, m), 5.09(1H, dd J=10.7, 3.5Hz), 6.48 and 6.59(1H, d, J=8.0-8.4Hz), 6.80-6.98(3H, m), 7.08-7.17(3H, m), 7.38 and 8.32(1H, t, J=5.7Hz)

Table D-130

Example 130

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$

R31			R32			R33		
H			Et			Et		
Reaction1								
Compound I-b11 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.250	1.000	0.68	25.00	30	nHx:EA =1:1	I-a130	0.200
Reaction2								
Compound I-a130(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.200	0.36	0.400	4.00	12	nHx:EA =1:1	I-b130	0.100	
Reaction3								
Compound I-b130(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.100	0.015	5.00	1	MC:MeOH =25:1		0.016	18.41	
ESI-MS(M^++1):587								
1H-NMR($CDCl_3$): (two rotamers) d 0.54, 0.81, 0.87 and 0.93(6H, d, J=6.0-6.8Hz), 1.12 and 1.19(6H, t, J=6.8-7.2Hz), 1.36 and 1.39(9H, s), 2.25-2.43(1H, m), 2.60-2.74(1H, m), 2.78-2.99(2H, m), 3.16-3.50(4H,m), 3.56-3.80(2H, m), 4.53-4.74(2H, m), 4.83-4.88 and 4.99-5.11(2H, m), 6.48 and 6.63(1H, d, J=7.9Hz), 6.80-6.85 and 6.96-7.18(6H, m), 7.46-7.49 and 7.58-								

Table D-131

Example 131

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$

R31	R32	R33
Me	Et	Et

Reaction1

Compund I-b11 (g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.340	1.000	0.68	25.00	30	nHx:EA =1:1	I-a131	0.170

Reaction2

Compound I-a131(g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.170	0.31	0.014	4.00	12	nHx:EA =1:1	I-b131	0.080

Reaction3

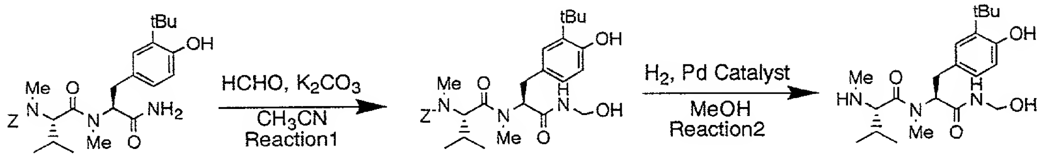
Compound I-b131(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.080	0.012	4.00	1	MC:MeOH =25:1	0.040	18.97

ESI-MS(M^++1):601

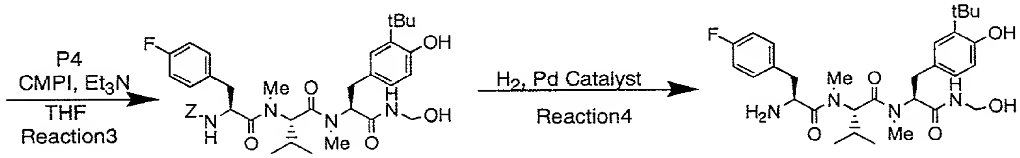
1H-NMR($CDCl_3$):(two rotamers) δ 0.64(1H, d, J=6.4Hz), 0.85-0.97(7H, m), 1.10-1.19(4H, m), 1.33 and 1.37(9H, s), 2.25-2.43(1H, m), 2.29 and 2.31(3H, s), 2.67-2.86(3H, m), 3.12-3.65 and 3.74-3.81(6H, m), 4.52-4.72(2H, m), 4.87-4.92 and 5.09-5.19(2H, m), 6.45 and 6.59(1H, d, J=8.0 and 8.4Hz), 6.78(2/3H, dd, J=7.9, 1.5Hz), 6.90-6.98(7/3H, m), 7.04(2/3H, d, J=1.5Hz), 7.10-7.16(7/3H, m), 7.50 and 7.90(1H, t, J=6.3 and 6.0Hz)

Scheme 5 shows the synthesis process of Example 132.

Scheme 5: Synthesis process of Example 132



Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 I-a132 I-b132



I-c132 Example 132

The synthesis process in scheme 5 is explained below.

Reaction step 1)

To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 in CH_3CN, 38% HCHO and K_2CO_3 were added and stirred at room temperature. The reaction mixture was mixed with a saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a132.

Reaction step 2)

To a solution of Compound I-a132 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room

temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b132.

Reaction step 3)

To a solution of Compound I-b132, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c132.

Reaction step 4)

To a solution of Compound I-c132 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-132 shows Example conducted according to Scheme 5.

Table D-132

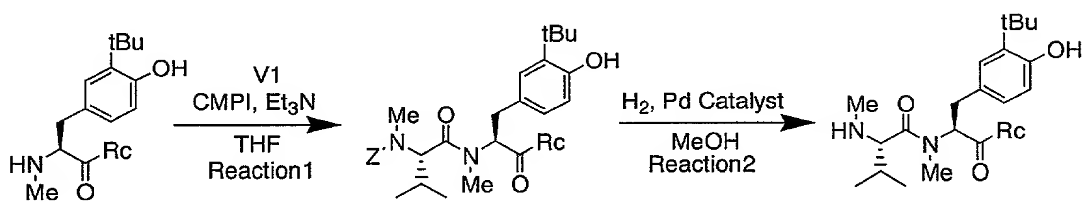
Example 132

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$

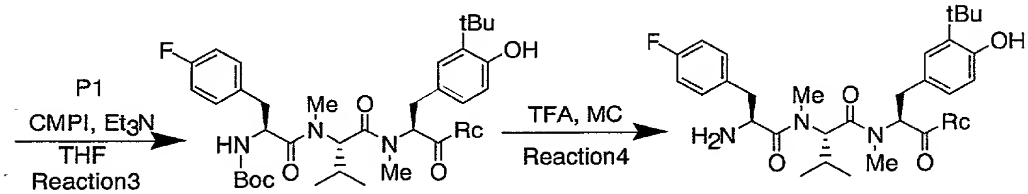
R31			R32			R33		
H			Me			Me		
Reaction1								
Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	HCHO (ml)	K_2CO_3 (g)	CH_3CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.000	3.00	1.100	71.00	2	nHx:EA:MC =1:3:1	I-a132	2.000	
Reaction2								
Compound I-a132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.950	0.290	50.00	1	EA:MeOH =7:1		I-b132	0.730	
Reaction3								
Compound I-b132(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	0.880	0.700	0.50	35.00	4	nHx:EA =1:4	I-c132	0.700
Reaction4								
Compound I-c132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	0.110	10.00	4	MC:MeOH =20:1		0.410	16.64	
ESI-MS(M^++1):559								
1H-NMR($CDCl_3$): (two rotamers) δ 0.49, 0.74, 0.78 and 0.91(6H, d, J=5.9-6.6Hz), 1.33 and 1.37(9H, s), 2.20-2.97(4H, m),2.54, 2.81 and 3.00(6H, s),3.16 and 3.35(1H, dd, J=13.7-15.1, 6.2-6.5Hz),3.71 and 3.85(1H, dd, J=8.1-9.4, 4.5-5.0Hz), 4.64 and 4.69(2H, d, J=6.0-6.4Hz), 4.79 and 5.06(1H, d, J=10.2-10.6Hz), 5.00 and 5.36(1H, dd, J=9.2, 5.5Hz), 6.43 and 6.64(1H, d, J=7.8Hz), 6.71-7.12(6H, m)								

Scheme 6 shows the synthesis process of Examples 133-135.

Scheme 6: Synthesis process of Examples 133-135



T13~15 I-a133~135 I-b133~135



I-c133~135

Rc in the above Scheme indicates the substituent shown in Tables D-133 to D-135.

The synthesis process in scheme 6 is explained below.

Reaction step 1)

To solutions of Compounds T13 to T15, Compound V1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a133 to I-

a135.

Reaction step 2)

To solutions of Compound I-a133 to I-a135 in methanol, palladium hydroxide/carbon was added and stirred in a hydrogen atmosphere at room temperature. The reaction mixtures were filtered and the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b133 to I-b135.

Reaction step 3)

To solutions of Compounds I-b133 to I-b135, Compound P1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c133 to I-c135.

Reaction step 4)

To solutions of Compounds I-c133 to I-c135 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were neutralized by the addition of a saturated aqueous NaHCO3 solution, extracted with dichloromethane, washed with saturated brine,

dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Tables D-133 to D-135 show Examples conducted according to Scheme 6.

Table D-133

Example 133

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-morpholine								
Reaction1								
Compound T13(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.490	0.720	0.50	20.00	20	nHx:EA = 1:1	I-a133	0.900
Reaction2								
Compound I-a133(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.900	0.100	20.00	20	MC:MeOH = 20:1		I-b133	0.600	
Reaction3								
Compound I-b133(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.450	0.530	0.40	20.00	20	nHx:EA = 1:1	I-c133	0.850
Reaction4								
Compound I-c133 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.850	3.00	10.00	4	MC:MeOH = 20:1		0.600	19.77	
ESI-MS(M^++1):599								
1H-NMR($CDCl_3$): (two rotamers) δ 0.78 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.24(3H, s), 2.48-2.56(1H, m), 2.79-2.87(5H, m), 3.02-3.09(1H, m), 3.40-3.74(10H, m), 5.01-5.05(1H, J=10.0 Hz), 5.79-5.84(1H,m), 6.39 and 6.41(1H,d, J=7.9Hz), 6.74-6.77(1H,m), 6.99-7.18(6H,m)								

Table D-134

Example 134

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-(methylsulfonyl) piperazine								
Reaction1								
Compound T14(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	0.790	1.100	0.84	20.00	20	nHx:EA = 1:1	I-a134	1.500
Reaction2								
Compound I-a134 (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.500	0.300	20.00	20	MC:MeOH = 20:1		I-b134	0.900	
Reaction3								
Compound I-b134 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.520	0.430	0.38	15	2	nHx:EA = 1:1	I-c134	0.700
Reaction4								
Compound I-c134 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	3.00	10.00	4	MC:MeOH = 20:1		0.350	19.94	
ESI-MS(M^++1):677								
1H-NMR($CDCl_3$): (two rotamers) δ 0.79 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.52-2.69(4H, m), 2.73(3H, s), 2.75-2.89(7H, m), 3.01-3.16(4H, m), 3.58-3.78(1H, m), 5.03 and 5.07(1H,d, J=10.6 Hz), 5.75-5.81(1H, m), 6.42 and 6.45(1H, d, J=7.9Hz), 6.76-6.80(1H, m), 6.99-7.18(6H, m)								

Table D-135

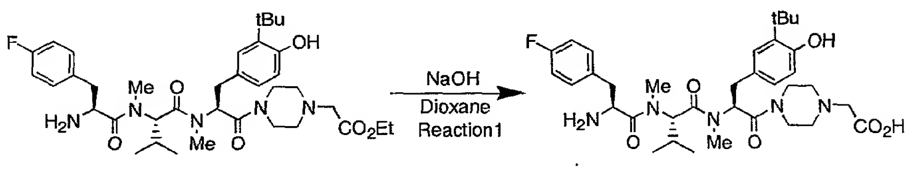
Example 135

Ethyl 2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl] propanoyl)piperazinyl]acetate

R								
ethyl-2-piperazinylacetate								
Reaction1								
Compound T15 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.643	0.547	0.527	0.50	16.00	16	nHx:EA= 2:3	I-a135	0.827
Reaction2								
Compound I-a135 (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.827	0.250	13.00	1	MC:MeOH =20:1		I-b135	0.645	
Reaction3								
Compound I-b135 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.645	0.458	0.413	0.40	12	16	nHx:EA= 2:3	I-c135	0.796
Reaction4								
Compound I-c135(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.796	2.00	5.00	1	MC:MeOH =30:1		0.430	17.1	
ESI-MS(M^++1):684								
1H-NMR($CDCl_3$): (two rotamers) δ 0.77 and 0.84(6H, d, J=6.4-6.8Hz),1.26(3H, t, J=7.1Hz),1.26(9H, s), 2.22-2.30(1H, m),2.47-2.54(1H, m),3.00-3.07(1H, m) 2.40, 2.81 and 3.18(6H, s), 3.54-3.73(5H, m), 4.18(2H, q, J=7.1Hz), 5.03(2H, d, J=10.4Hz), 5.85(1H, t, J=2.3Hz), 6.40(1H, d, J=7.9Hz), 6.72-6.75 (1H, dd, J=9.7, 1.9Hz), 7.00-7.26(5H, m)								

Scheme 7 shows the synthesis process of Example 136.

Scheme 7: Synthesis process of Example 136



Example 135 Example 136

Reaction step 1)

The compound obtained in Example 135 was added to a dioxane solution, mixed with a 2N-NaOH solution and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-136 shows Example conducted according to Scheme 7.

Table D-136

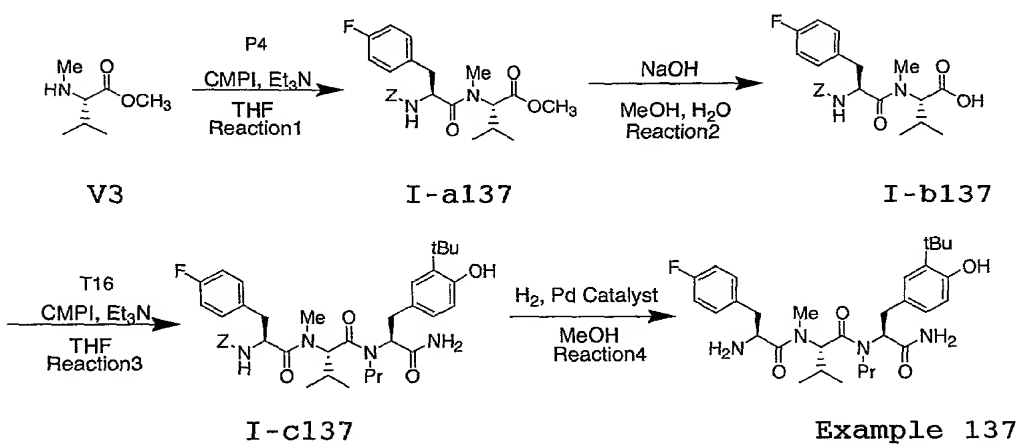
Example 136

2-[4-((2S)-2-{(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-3,N-dimethylbutanoylamino}-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetic acid

Reaction							
Compound of Example 135(g)	NaOH (g)	H_2O (ml)	Dioxane (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.375	0.400	5.00	5.00	16	MC:MeOH=20:1	0.200	14.97
ESI-MS(M^++1):656							
1H-NMR(CD3OD): (two rotamers) δ 0.78 and 0.82(6H, d, J=6.1Hz),1.27(9H, s), 2.12-2.29(1H, m), 2.74-3.12(8H, m),3.61-3.82(4H, m), 2.48, 2.94, 3.25 and 3.55(6H, s), 4.50-4.56(1H, q, J=10.5Hz), 5.02(1H, d, J=10.5Hz), 5.73(1H, t, J=7.9Hz), 6.74-6.78(1H, dd, J=9.4, 2.2Hz), 7.00-7.27(6H, m)							

Scheme 8 shows the synthesis process of Example 137.

Scheme 8: Synthesis process of Example 137



The synthesis process in scheme 8 is explained below.

Reaction step 1)

To a solution of Compound V3, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a137.

Reaction step 2)

To a solution of Compound I-a137 in methanol, NaOH and water were added and stirred at room temperature. The reaction mixture was mixed with a saturated aqueous NH_4Cl solution, concentrated under reduced pressure, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b137.

Reaction step 3)

To a solution of Compound I-b137, Compound T16 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography

(silica gel) to give Compound I-c137.

Reaction step 4)

To a solution of Compound 1-c137 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-137 shows Example conducted according to Scheme 8.

Table D-137

Example 137

Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH_2

Reaction1

Compound V3 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.146	3.000	2.410	2.20	28.00	12	nHx:EA =5:1	I-a137	1.877

Reaction2

Compound I-a137(g)	NaOH (g)	H_2O (ml)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
1.870	0.646	8.00	40.00	8	I-b137	1.710

Reaction3

Compound I-b137(g)	Compound T10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.710	0.709	0.976	0.88	14.00	12	nHx:EA =3:2	I-c137	0.610

Reaction4

Compound I-c137(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.400	0.080	16.00	1	MC:MeOH =25:1	0.128	22.7

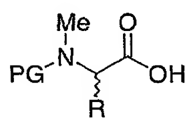
ESI-MS(M^++1):557

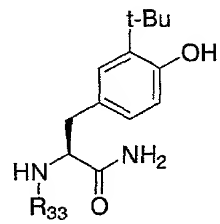
1H-NMR($CDCl_3$): δ 0.66(3H, d, J=6.6Hz), 0.80(3H, d, J=6.5Hz), 0.84(3H, t, J=7.4Hz), 1.33(9H, s), 1.43-1.59(2H, m), 2.20-2.28(1H, m), 2.53(1H, dd, J=13.5, 9.1Hz), 2.60-2.75(2H, m), 2.95(1H, dd, J=13.8, 4.8Hz), 3.01(3H, s), 3.20(1H, dd, J=14.1, 6.2Hz), 3.32(1H, dd, J=13.6, 10.9Hz), 3.52-3.63(1H, m), 3.89-3.93(1H, m), 4.21-4.28(1H, m), 4.89(1H, d, J=10.6Hz), 5.48(1H, brs), 6.51(1H, d, J=7.9Hz), 6.73(1H, dd, J=7.9, 1.9Hz), 6.82(1H, brs), 6.99-7.10(3H, m), 7.11-7.16(2H, m)

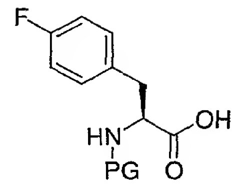
The processes of synthesizing Intermediates of Schemes 9-14 are shown below as Reference Examples. In addition, structural formulae of Intermediates of Examples 138-176 are shown in Tables C-3 and C-4.

Table C-3

Intermediates of Examples 138-176







I1:R=Et , I2:R=Et(D) T1: R33=H P1: PG=Z or Boc

I3:R=n-Pr, I4:R=n-Pr(D) T4: R33=Me P4: PG=Z or Boc

I5:R=s-Bu (commercial), I6:R=s-Bu(D)

I7:R=i-Bu (commercial), I8:R=i-Bu(D)

I9:R=Allyl, I10:R=Allyl(L,D-mixture)

I11:R=neo-Pentyl, I12:R=neo-Pentyl(D)

I13:R=CH_2CF_3(L,D-mixture)

I14:R=c-Hex, I15:R=c-Hex(D)

I16:R=CH_2c-Hex, I17:R=CH_2c-Hex(D)

I18:R=CH_2Ph, I19:R=CH_2Ph(D)

I20:R=CH_2Ph(4-F), I21:R=CH_2Ph(4-F)(D)

I22:R=CH_2Ph(4-Cl), I23:R=CH_2Ph(4-Cl)(D)

I24:R=CH_2Ph(4-OBn), I25: R=CH_2Ph(4-OBn)(D)

I26:R=CH_2(2-thienyl), I27: R=CH_2(2-thienly)(D)

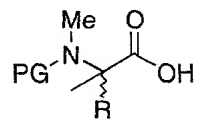
I28:R=CH_2c-Pr

I38:R=tBu

I29:N-Me-Phg-OMe, I30:N-Me-D-Phg-OMe

Table C-4

Intermediates of Examples 138-176 (continued)

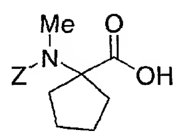


I31: R=CH_2Ph, I32: R=CH_2Ph(D)

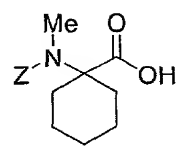
I33: R=i-Bu

I34: R=Et(D)

I35: R=i-Pr(D)



I36



I37

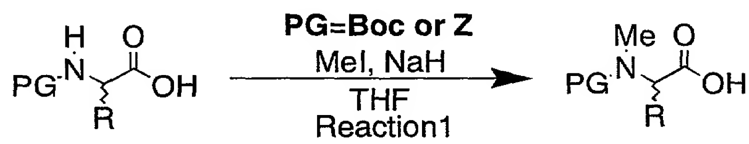
In Tables C-3 and C-4, "commercial" means that the compound is commercially available, "(D)" means a D-amino acid in stereochemistry and those which are not indicated as (D) are L-amino acids. PG in the Intermediate (I) means Z or Boc.

Reference Example 21

Synthesis of Intermediates I1 to I28

The synthesis scheme is shown below.

Synthesis scheme of Intermediates I1 to I28



Z or Boc-Amino acid I1~28

The synthesis process of Intermediates I1 to I28 is explained below.

Reaction step 1)

To solutions of Z- and Boc-protected amino acids in THF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I1 to I28.

Results are shown in Tables E-10 to E-35.

Table E-10

Intermediates I1: Z-N-Me-Abu-OH

R						
Et						
Reaction						
Z-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	4.20	1.340	40.00	15	MC:MeOH =10:1	1.400

Table E-11

Intermediate I2: Boc-N-Me-D-Abu-OH

R						
Et:D						
Reaction						
Boc-(D)-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.750	1.83	0.738	18.00	48	MC:MeOH =8:1	0.810

Table E-12

Intermediate I3: Z-N-Me-Nva-OH

R						
n-Pr						
Reaction						
Z-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	5.00	0.960	30.00	24	MC:MeOH =10:1	2.090

Table E-13

Intermediate I4: Boc-N-Me-D-Nva-OH

R						
n-Pr:D						
Reaction						
Boc-(D)-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.87	0.552	25.00	40	MC:MeOH =10:1	1.000

Table E-14

Intermediate I6: Boc-N-Me-D-Ile-OH

R						
s-Bu:D						
Reaction						
Boc-(D)-Ile-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.500	1.35	0.866	17.00	12	MC:MeOH =10:1	0.490

Table E-15

Intermediate I8: Boc-N-Me-D-Leu-OH

R						
i-Bu:D						
Reaction						
Boc-(D)-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.49	1.600	17.00	12	MC:MeOH =15:1	0.960

Table E-16

Intermediate I9:

(2S)-2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl						
Reaction						
(2S)-2-[(tert-butoxy)carbonylamino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.660	1.79	1.150	12.00	12	MC:MeOH =10:1	0.570

Table E-17

Intermediate I10:

2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl: D,L-mixture						
Reaction						
2-[(tert-butoxy)carbonyl - amino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.656	7.67	4.924	51.00	12	MC:MeOH =15:1	2.360

Table E-18

Intermediate I11:BOC-N-Me-Leu(γ-Me)-OH

R						
neo-Pent						
Reaction						
BOC-Leu(gamma-Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.930	4.86	3.120	40.00	48	MC:MeOH =10:1	1.500

Table E-19

Intermediate I12: BOC-N-Me-D-Leu(γ-Me)-OH

R						
neo-Pent:D						
Reaction						
BOC-(D)-Leu(gamma-Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.50	1.630	20.00	24	MC:MeOH =10:1	1.110

Table E-20

Intermediate I13: 2-[N-(phenylmethoxy)carbonyl-methylamino]-4,4,4-trifluorobutanoic acid

R						
CH_2CF_3:L,D-mixture						
Reaction						
Z-2-amino-4,4,4-trifluorobutanoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.75	1.61	1.03	20.00	12	MC:MeOH =10:1	0.567

Table E-21

Intermediate I14: Boc-N-Me-Chg-OH

R						
c-Hex						
Reaction						
Boc-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.60	2.300	40.00	20	MC:MeOH =30:1	1.500

Table E-22

Intermediate I15: Boc-N-Me-D-Chg-OH

R						
c-Hex:D						
Reaction						
Boc-(D)-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.70	1.740	30.00	20	MC:MeOH =30:1	1.150

Table E-23

Intermediate I16: Boc-N-Me-Cha-OH

R						
CH_2c-Hex						
Reaction						
Boc-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.40	1.100	23.00	18	MC:MeOH =10:1	1.300

Table E-24

Intermediate I17: Boc-N-Me-D-Cha-OH

R						
CH_2c-Hex:D						
Reaction						
Boc-(D)-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.72	0.552	11.50	18	MC:MeOH =10:1	1.000

Table E-25

Intermediate I18: Boc-N-Me-Phe-OH

R						
CH_2Ph						
Reaction						
Boc-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-26

Intermediate I19: Boc-N-Me-D-Phe-OH

R						
CH_2Ph:D						
Reaction						
Boc-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.890	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-27

Intermediate I20: Boc-N-Me-Phe(4-F)-OH

R						
$CH_2Phe(4-F)$						
Reaction						
Boc-Phe-(4-F)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
15.000	27.00	6.360	180.00	24	MC:MeOH =10:1	15.000

Table E-28

Intermediate I21: Boc-N-Me-D-Phe(4-F)-OH

R						
$CH_2Phe(4-F):D$						
Reaction						
Boc-(D)-Phe(4-F)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.76	0.424	12.00	18	MC:MeOH =10:1	1.000

Table E-29

Intermediate I22: Boc-N-Me-Phe(4-Cl)-OH

R						
$CH_2Ph(4\text{-}Cl)$						
Reaction						
Boc-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.32	0.800	40.00	18	MC:MeOH =20:1	1.630

Table E-30

Intermediate I23: Boc-N-Me-D-Phe(4-Cl)-OH

R						
$CH_2Ph(4\text{-}Cl)\text{:}D$						
Reaction						
Boc-(D)-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.401	20.00	18	MC:MeOH =20:1	0.781

Table E-31

Intermediate I24: Boc-N-Me-Phe(4-OBn)-OH

R						
$CH_2Ph(4\text{-}OBn)$						
Reaction						
Boc-Phe(4-OBn)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.500	3.35	0.808	50.00	36	MC:MeOH =20:1	2.590

Table E-32

Intermediate I25: Z-N-Me-D-Phe(4-OBn)-OH

R						
CH_2Ph(4-OBn):D						
Reaction						
Z-(D)-Phe(4-OBn)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	2.51	0.592	40.00	36	MC:MeOH =20:1	2.060

Table E-33

Intermediate I26: Boc-N-Me-Ala(β-2-thienyl)-OH

R						
CH_2(2-Thienyl)						
Reaction						
Boc-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	0.916

Table E-34

Intermediate I27: Boc-N-Me-D-Ala(β-2-thienyl)-OH

R						
CH_2(2-Thienyl):D						
Reaction						
Boc-(D)-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	1.040

Table E-35

Intermediate I28: Z-N-Me-Ala(β-c-Pr)-OH

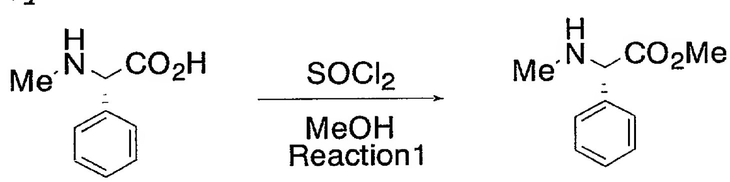
R						
CH_2c-Propyl						
Reaction						
Z-N-Ala(beta-c-Pr)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.84	0.680	15.00	15	MC:MeOH =10:1	1.160

Reference Example 22

Synthesis of Intermediate I29

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I29



N-Me-Phg-OH I29

The synthesis process of Intermediate I29 is explained below.

Reaction step 1)

To a solution of N-Me-Phg-OH in methanol, $SOCl_2$ was slowly added dropwise under cooling and then stirred under reflux. The reaction mixture was concentrated under reduced pressure to give crude Compound I29.

Result is shown in Table E-36.

Table E-36

Intermediate I29: N-Me-Phg-OMe

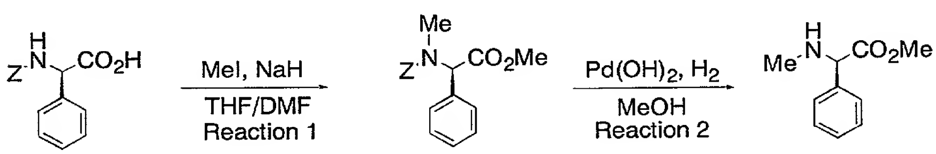
Reaction				
N-Me-Phg-OH (g)	$SOCl_2$ (ml)	MeOH (ml)	Reaction time (hr)	Amount (g)
2.000	1.32	20.00	3.00	2.000

Reference Example 23

Synthesis of Intermediate I30

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I30



Z-D-Phg-OH Z-N-Me-D-Phg-OMe I30

The synthesis process of Intermediate I30 is explained below.

Reaction step 1)

To a solution of Z-D-Phg-OH and CH_3I in THF and DMF, NaH was slowly added dropwise and then stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Z-N-Me-D-Phg-OMe.

Reaction step 2)

To a solution of Z-N-Me-D-Phg-OMe in methanol, palladium hydroxide/carbon was added and stirred in a hydrogen atmosphere at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel), giving Compound I30.

Result is shown in Table E-37.

Table E-37

Intermediate I30: N-Me-D-Phg-OMe

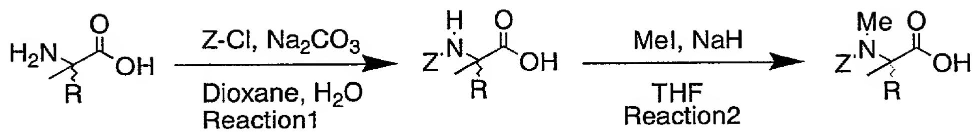
R							
Ph :D							
Reaction1							
Z-N-Me-(D)-Phg-OH (g)	Methyl iodide (ml)	NaH (g)	THF/DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	3.49	0.842	20.00 (10.00/10.00)	16	nHx:EA=5:1	Z-N-Me-(D)-Phg-OMe	2.200
Reaction2							
Z-N-Me-(D)-Phg-OMe(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)		
2.200	0.330	40.00	12	nHx:EA=5:1	1.240		

Reference Example 24

Synthesis of Intermediates I31-I35

The synthesis scheme is shown below.

Synthesis scheme of Intermediates I31-I35



α-Me-Amino acid Z-α-Me-Amino acid I31~I35

The synthesis process of Intermediates I31 to I35 is explained below.

Reaction step 1)

To solutions of α-Me-amino acids and Na_2CO_3 in dioxane and water, Z-Cl was slowly added dropwise under cooling while stirring. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel), giving Z-α-Me-amino acids.

Reaction step 2)

T solutions of the Z-α-Me-Amino acid and CH_3I in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to giving Compounds I31 to I35.

Results are shown in Tables E-38 to E-42.

Table E-38

Intermediate I31: Z-N-Me-α-Me-Phe-OH

R								
CH_2Ph								
Reaction1								
alpha-Me-Phe-OH (g)	Z-Cl (ml)	Na_2CO_3 (g)	Dioxane (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-Phe-OH	0.890
Reaction2								
Z-alpha-Me-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.890	1.40	0.340	28.00	15	MC:MeOH =10:1		1.180	

Table E-39

Intermediate I32: Z-N-Me-α-Me-D-Phe-OH

R								
CH_2Ph:D								
Reaction1								
alpha-Me-(D)-Phe-OH (g)	Z-Cl (ml)	Na_2CO_3 (g)	Dioxane (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-(D)-Phe-OH	0.810
Reaction2								
Z-alpha-Me-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.810	1.40	0.340	28.00	15	MC:MeOH =10:1		1.050	

Table E-40

Intermediate I33: Z-N-Me-α-Me-Leu-OH

R								
i-Bu								
Reaction1								
alpha-Me-Leu-OH (g)	Z-Cl (ml)	Na_2CO_3 (g)	Dioxane (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.970	2.10	2.140	30.00	20.00	24	MC:MeOH =10:1	Z-alpha-Me-Leu-OH	2.000
Reaction2								
Z-alpha-Me-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
2.000	4.40	2.000	35.00	12	MC:MeOH =10:1		1.780	

Table E-41

Intermediate I34: Z-N-Me-α-Me-D-Abu-OH

R								
CH_2CH_3 : D								
Reaction1								
alpha-Me-(D)-Abu-OH (g)	Z-Cl (ml)	Na_2CO_3 (g)	THF (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.36	0.450	10.00	2.00	3	MC:MeOH =10:1	Z-alpha-Me-(D)-Et-OH	0.177
Reaction2								
Z-alpha-Me-(D)-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.750	0.42	0.190	10.00	12	MC:MeOH =10:1		0.152	

Table E-42

Intermediate I35: Z-N-Me-α-Me-D-Val-OH

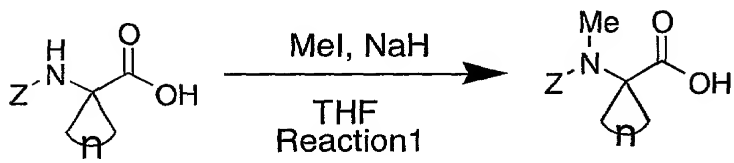
R								
i-Pr:D								
Reaction1								
alpha-Me-(D)-Val-OH (g)	Z-Cl (ml)	Na_2CO_3 (g)	Dioxane (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.31	1.454	4.00	4.00	12	MC:MeOH =15:1	Z-alpha-Me-(D)-Val-OH	0.170
Reaction2								
Z-alpha-Me-(D)-Val-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.170	0.40	0.128	3.00	12	MC:MeOH =10:1		0.170	

Reference Example 25

Synthesis of Intermediate I36, I37

The synthesis scheme is shown below.

Synthesis scheme of Intermediates I36 and I37



Spiro-cyclic-Amino acid I36~37

The synthesis process of Intermediates I36 and I37 is explained below.

Reaction step 1)

To solutions of a spiro-cyclic-amino acids and CH_3I in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I36 and I37.

Results are shown in Tables E-43 and E-44.

Table E-43

Intermediate I36:

1-[N-methyl(phenylmethoxy)carbonylamino]cyclopentanecarboxylic acid

Reaction						
Z-1-amino-1-cyclopentanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.79	0.912	26.00	18	MC:MeOH =20:1	1.730

Table E-44

Intermediate I37:

1-[N-methyl(phenylmethoxy)carbonylamino]cyclohexanecarboxylic acid

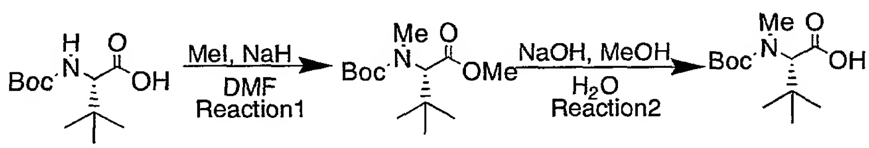
Reaction						
Z-1-amino-1-cyclohexanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	7.19	1.730	80.00	18	MC:MeOH =20:1	4.190

Reference Example 26

Synthesis of Intermediate I38

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I38



Boc-Tle-OH Boc-N-Me-Tle-OMe I38

The synthesis process of Intermediate I38 is explained below.

Reaction step 1)

To a solution of Boc-Tle-OH in DMF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixture was mixed with 1N HCl, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give Boc-N-Me-Tle-OMe.

Reaction step 2)

To a solution of Boc-N-Me-Tle-OMe in methanol and water, NaOH was added and stirred at room temperature. The reaction mixture was adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the

thus obtained residue was purified by column chromatography (silica gel), giving Intermediate I38.

Result is shown in Table E-45.

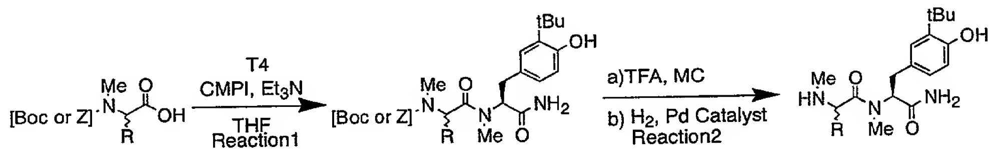
Table E-45

Intermediate I38: Boc-N-Me-Tle-OH

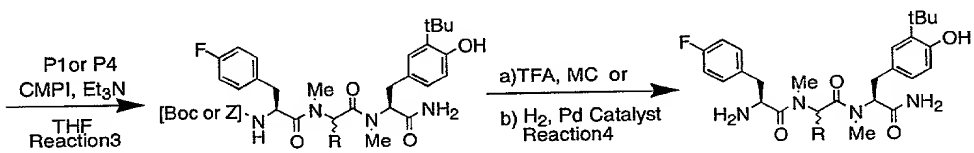
Reaction1						
Boc-Tle-OH (g)	Methyl iodide (ml)	NaH (g)	DMF (ml)	Reaction time (hr)	Product	Amount (g)
1.000	2.70	0.865	18.00	16	Boc-N-Me-Tle-OMe	1.180
Reaction2						
Boc-N-Me-Tle-OMe (g)	NaOH (g)	MeOH (ml)	H_2O (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.180	0.550	10.00	2.00	22	MC:MeOH=10:1	0.900

Scheme 9 shows the synthesis process of Examples 138-165.

Scheme 9: Synthesis process of Examples 138-165



I1~28 I-a138~165 I-b138~165



I-c138~165

The synthesis process in scheme 9 is explained below.

Reaction step 1)

To solutions of Compound T4, Compounds I1 to I28 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a138 to I-a165.

Reaction step 2-a)

To solutions of Compounds I-a in dichloromethane, TFA was added under cooling and stirred at room temperature.

The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b.

Reaction step 2-b)

To solutions of Compounds I-a in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b.

Reaction step 3)

To solutions of Compounds I-b138 to I-b165, Compound P1 or P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c138 to I-c165.

Reaction step 4-a)

To solutions of Compounds I-c in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Reaction step 4-b)

To solutions of Compounds I-c in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Compounds which were synthesized in Examples according to Scheme 9 are shown in Tables D-138 to D-165. In the tables "A" indicated after the Example number means "less polar isomer" and "B" means "more polar isomer". For example, Compound of Example 150A is "less polar isomer" of Phe(4-F)-N-Me-Ala(β-CF_3)-N-Me-Tyr(3-tBu)-NH_2 and Compound of Example 150B is "more polar isomer" of Phe(4-F)-N-Me-Ala(β-CF_3)-N-Me-Tyr(3-tBu)-NH_2.

Table D-138

Example 138

Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH_2

R								
Et								
Reaction1								
Compound T4 (g)	Compound I1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.960	0.980	0.90	30.00	12	nHx:EA=1:2	I-a138	1.420
Reaction2-b								
Compound I-a138(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.400	0.430	28.00	2	MC:MeOH =15:1	I-b138		0.950	
Reaction3								
Compound I-b138(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.890	0.860	0.780	0.70	5.00	72	nHx:EA =1:1	I-c138	0.720
Reaction4-a								
Compound I-c138(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.720	1.80	9.00	3	MC:MeOH= 15:1	0.420		17.07	
ESI-MS(M^++1):515								
1H-NMR(CD_3OD):(two rotamers) δ 0.55 and 0.88(3H, t, J=7.2-7.6Hz), 1.39 and 1.44(9H, s), 1.56-1.85(2H, m), 2.23, 2.62, 2.91 and 2.98(6H, s), 2.56-3.01(4H, m), 3.26(1H, dt, J=3.0-4.7, 13.9-15.4Hz), 3.78 and 3.97(1H, dd, J=8.4, 5.1Hz), 5.28 and 5.55(1H, dd, J=7.8-11.6, 4.8-6.0Hz),6.59 and 6.74(1H, d, J=8.0Hz), 6.69-7.30(6H, m)								

Table D-139

Example 139

Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH_2

R
Et:D

Reaction1

Compound T4 (g)	Compound I2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.800	0.950	0.85	60.00	12	nHx:EA =1:2	I-a139	1.100

Reaction2-a

Compound I-a139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.100	4.90	26.00	1	MC:MeOH =8:1	I-b139	0.770

Reaction3

Compound I-b139(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.750	0.670	0.60	44.00	72	nHx:EA =1:2	I-c139	1.310

Reaction4-a

Compound I-c139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.300	4.20	21.00	2	MC:MeOH= 15:1	0.620	19.96

ESI-MS(M^++1):515

1H-NMR(CD_3OD): δ 0.48(3H, t, J=7.5Hz), 1.36(9H, s), 1.38-1.43(2H, m), 2.59 and 2.87(3H, s), 2.73(1H, dd, J=13.2, 7.5 Hz), 2.81-2.92(2H, m), 3.02 and 3.14(3H, s), 3.37(1H, dd, J=15.0,6.1Hz), 3.93(1H, t, J=6.8-7.1Hz), 4.82(1H, t, J=7.7Hz), 5.34(1H, brs),5.50(1H, dd, J=11.3, 5.9Hz), 6.42(1H, brs),6.57(1H, d, J=7.8Hz), 6.88(1H, dd, J=7.7, 2.0Hz), 6.96(2H, t, J=8.6Hz), 7.08(1H, d, J=2.3Hz), 7.13(2H, m)

Table D-140

Example 140

Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH_2

R
n-Pr

Reaction1

Compound T4 (g)	Compound I3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.830	0.800	0.847	0.84	30.00	24	nHx:EA =1:2	I-a140	1.372

Reaction2-b

Compound I-a140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.372	0.200	80.00	2	MC:MeOH =10:1	I-b140	0.895

Reaction3

Compound I-b140(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c140	0.744

Reaction4-b

Compound I-c140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.727	0.200	50.00	2	MC:MeOH =10:1	0.450	19.05

ESI-MS(M^++1):529

1H-NMR($CDCl_3$+CD_3OD): (two rotamers) δ 0.20 and 0.70-1.20(3H, m), 0.65 and 0.75(3H, t, J=6.9Hz), 1.50-1.70(1H, m), 1.33 and 1.38(9H, s), 2.30 and 2.69(3H, s), 2.47 and 2.70(2H, m), 2.72(3H,s), 2.80 and 2.92(2H, m), 3.65 and 3.85(1H,m), 4.83(1H, m), 5.84(1H, m), 6.48(1H, d, J=9.69Hz), 6.70-6.82(1H, m), 6.90-7.20(5H, m)

Table D-141

Example 141

Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH_2

R
n-Pr:D

Reaction1

Compound T4 (g)	Compound I4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.650	0.547	0.665	0.70	20.00	16	nHx:EA =1:2	I-a141	0.670

Reaction2-a

Compound I-a141(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.670	1.50	10.00	2	MC:MeOH =10:1	I-b141	0.500

Reaction3

Compound I-b141(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.490	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c141	0.680

Reaction4-b

Compound I-c141(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.680	0.100	20.00	2	MC:MeOH =10:1	0.358	22.27

ESI-MS(M^++1):529

1H-NMR($CDCl_3$+CD_3OD): (two rotamers) δ 0.65-0.90(2H, m), 0.75(3H, t, J=6.9Hz), 1.20-1.50(2H, m), 1.37 and 1.39(9H, s), 2.75(2H, brs), 2.85 and 2.87(3H,s), 2.80(1H, m), 3.00 and 3.02(3H, s), 3.45(1H, m), 3.95(1H, t, J=7.2Hz), 4.91(1H, t, J=7.5Hz), 5.40(2H, m, brs), 6.40(1H, brs), 6.60(1H, d, J=9.3Hz), 6.37(1H, d, 9.3Hz), 6.90-7.18(5H, m)

Table D-142

Example 142

Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH_2

R								
s-Bu								
Reaction1								
Compound T4 (g)	Compound I5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.750	1.000	0.910	0.83	19.00	12	nHx:EA= 2:3	I-a142	1.350
Reaction2-b								
Compound I-a142 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.300	0.190	50.00	2	MC:MeOH =20:1	I-b142		0.920	
Reaction3								
Compound I-b142 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	0.830	0.750	0.67	25.00	12	nHx:EA=2:3	I-c142	1.170
Reaction4-a								
Compound I-c142 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
1.150	2.75	13.00	3	MC:MeOH =20:1	0.710		19.710	
ESI-MS(M^++1):543								
1H-NMR($CDCl_3$ + CD_3OD):(two rotamers) δ 0.38, 0.81, 0.85 and 0.88(6H, d, J=6.0-6.5Hz), 0.93-1.02(1H, m), 1.18-1.29(1H, m), 1.34 and 1.39(9H, s), 1.97-2.11(1H, m), 2.38-2.93(3H, m), 2.50, 2.86, 2.95 and 3.00(6H, s), 3.11-3.18(1H, m), 3.69 and 3.84(1H, dd, J=8.0-8.9, 4.0-5.5Hz), 4.91-4.96 and 5.02-5.14(4/3H, m), 5.45(2/3H, dd, J=10.2, 5.7Hz), 6.48(2/3H, d, J=7.9Hz), 6.65-6.71(1H, m), 6.91-7.12(16/3H, m)								

Table D-143

Example 143

Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH_2

R								
s-Bu:D								
Reaction1								
Compound T4 (g)	Compound I6 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.420	0.490	0.510	0.46	10.00	12	nHx:EA =2:3	I-a143	0.330
Reaction2-a								
Compound I-a143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
0.310	0.94	4.70	3	MC:MeOH = 10:1	I-b143		0.240	
Reaction3								
Compound I-b143 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.240	0.220	0.200	0.18	6.00	12	nHx:EA =2:3	I-c143	0.340
Reaction4-a								
Compound I-c143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.330	1.20	6.00	4	MC:MeOH = 10:1	0.140		23.200	
ESI-MS(M^++1):543								
1H-NMR($CDCl_3$): δ 0.27(3H, d, J=6.8Hz), 0.67-0.80(4H, m), 0.88-0.97(1H, m), 1.36(9H, s), 1.74-1.85(1H, m), 2.71(1H, dd, J=13.9, 7.2Hz), 2.84-3.00(2H, m), 2.96(3H, s), 3.12(3H, s), 3.35(1H, dd, J=14.6, 5.2Hz), 3.96(1H, t, J=7.0Hz), 4.79(1H, d, J=11.0Hz), 5.46(1H, dd, J=11.5, 5.4Hz), 5.50(1H, brs), 6.35(1H, brs), 6.58(1H, d, J=8.0Hz), 6.90-7.05(4H, m), 7.12-7.16(2H, m)								

Table D-144

Example 144

Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH_2

R
i-Bu

Reaction1

Compound T4 (g)	Compound I7 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.747	1.000	0.910	0.83	19.00	12	nHx:EA=2:3	I-a144	1.320

Reaction2-b

Compound I-a144 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	0.190	50.00	2	MC:MeOH =20:1	I-b144	0.940

Reaction3

Compound I-b144 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.940	0.850	0.760	0.69	25.00	12	nHx:EA =2:3	I-c144	1.230

Reaction4-a

Compound I-c144 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.210	2.90	14.50	3	MC:MeOH =20:1	0.750	19.380

ESI-MS(M^++1):543

1H-NMR(CD_3OD):(two rotamers) δ 0.66, 0.73, 0.94 and 0.96(6H, d, J=6.0-6.6Hz),1.37 and 1.40(9H, s), 1.40-1.52(2H, m), 1.55-1.68(1H, m), 2.26 and 2.65(3H, s), 2.53-2.69(1H, m), 2.69-3.00(1H, m),2.86 and 3.00(3H, s), 3.09-3.29(1H, m),3.72-3.78 and 3.90-3.94(1H, m), 4.56-4.64(1H, m),4.94-5.06(1H, m), 5.39-5.52(1H, m), 6.55-6.78(2H, m), 6.94-7.30(5H, m)

Table D-145

Example 145

Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH_2

R
i-Bu:D

Reaction1

Compound T4 (g)	Compound I8 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.810	0.960	1.000	0.91	25.00	12	nHx:EA=2:3	I-a145	1.450

Reaction2-a

Compound I-a145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.430	4.60	23.00	3	MC:MeOH =5:1	I-b145	1.140

Reaction3

Compound I-b145 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.140	1.010	0.910	0.83	25.00	12	nHx:EA=2:3	I-c145	0.940

Reaction4-a

Compound I-c145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.920	2.20	11.00	3	MC:MeOH =5:1	0.60	21.40

ESI-MS(M^++1):543

1H-NMR($CDCl_3$): δ 0.72(3H, d, J=4.3Hz), 0.73(3H, d, J=4.1Hz), 0.81-0.92(2H, m), 1.24-1.30(1H, m), 1.36(9H, s), 2.73-2.90(3H, m), 2.84(3H, s), 2.99(3H, s), 3.30(1H, dd, J=14.6, 5.6Hz), 3.96(1H, t, J=7.2Hz), 5.02(1H, dd, J=9.9, 4.9Hz), 5.44(1H, dd, J=10.9, 5.6Hz), 5.63(1H, brs), 6.38(1H, brs), 6.57(1H, d, J=8.4Hz), 6.85(1H, dd, J=7.8, 1.9Hz), 6.91-7.01(3H, m), 7.09-7.13(2H, m)

Table D-146

Example 146

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide

R
Allyl

Reaction1

Compound T4 (g)	Compound I9 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.573	0.630	0.700	0.64	14.00	12	nHx:EA=2:3	I-a146	0.900

Reaction2-a

Compound I-a146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.870	2.90	14.0	3	MC:MeOH=10:1	I-b146	0.660

Reaction3

Compound I-b146 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.620	0.560	0.51	17.00	12	nHx:EA =2:3	I-c146	0.570

Reaction4-a

Compound I-c146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.550	1.35	5.40	3	MC:MeOH=10:1	0.36	17.750

ESI-MS(M^{+}+1):527

1H-NMR($CDCl_3$): (two rotamers) δ 0.97-1.04(1/2H, m), 1.34 and 1.36(9H, s), 2.12-2.24(1/2H, m), 2.32-2.75(2H, m), 2.34 and 2.66(3H, s), 2.84-2.99(2H, m), 2.97(3H, s), 3.07-3.18(1H, m), 3.62-3.66 and 3.83-3.87(1H, m), 4.80-5.09(3H, m), 5.25-5.33 and 5.63-5.76(1H, m), 5.35-5.46(1H, m), 5.39(1H, brs), 6.06(0.5H, brs), 6.41 and 6.58(1H, d, J=8.2 and 8.0Hz), 6.74 and 6.83(1H, dd, J=7.9, 1.9Hz), 6.92-7.00(2H, m), 7.03-7.14(3H, m), 7.36(1/2H, brs)

Table D-147

Example 147

(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-N-methylpent-4-enamide

R								
Allyl:D								
Reaction1								
Compound T4 (g)	Compound I10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.180	1.300	1.440	1.30	30.00	12	nHx:EA =1:1	I-a147	0.340
Reaction2-a								
Compound I-a147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.330	1.10	5.00	3	MC:MeOH=7:1		I-b147	0.270	
Reaction3								
Compound I-b147 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.220	0.30	6.00	12	nHx:EA =2:3	I-c147	0.370
Reaction4-a								
Compound I-c147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	1.30	5.00	3	MC:MeOH=7:1		0.24	20.320	
ESI-MS(M^++1):527								
1H-NMR($CDCl_3$): δ 1.35(9H, s), 1.99-2.16(2H, m), 2.64-2.72(1H, m), 2.79-2.89(2H, m), 2.87(3H, s), 2.97(3H, s), 3.31(1H, d, J=15.3, 5.9Hz), 3.90(1H, t, J=7.0Hz), 4.87-4.93(2H, m), 5.01(1H, dd, J=9.0, 6.7Hz), 5.16-5.29(1H, m), 5.44(1H, dd, J=10.5, 6.0Hz), 5.50(1H, brs), 6.37(1H, brs), 6.57(1H, d, J=7.8Hz), 6.85(1H, dd, J=7.9, 1.9Hz), 6.92-6.98(2H, m), 7.02(1H, d, J=2.2Hz), 7.09-7.13(2H, m)								

Table D-148

Example 148

Phe(4-F)-N-Me-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2

R
neo-Pent

Reaction1

Compound T4 (g)	Compound I11 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.780	0.770	0.35	25.00	48	nHx:EA =1:2	I-a148	0.850

Reaction2-a

Compound I-a148(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	2.50	12.50	4	MC:MeOH=9:1	I-b148	0.600

Reaction3

Compound I-b148(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.580	0.470	0.42	30.00	12	nHx:EA:MC =1:2:1	I-c148	0.950

Reaction4-b

Compound I-c148(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.950	0.140	13.00	3	MC:MeOH=20:1	0.58	20.96

ESI-MS(M^++1):557

1H-NMR(CD_3OD):(two rotamers) δ 0.71 and 0.99(9H, s), 1.43 and 1.46(9H, s), 1.28-1.40(2H, m), 2.43, 2.81, 2.97 and 3.07(6H, s), 2.23-3.04(4H, m), 3.25-3.28(1H, m), 3.79(2/3H, m), 3.92(1/3H, dd, J=9.8, 4.6Hz), 5.58 and 5.53(1H, dd, J=6.9-8.2, 4.8-6.9Hz), 6.61 and 6.80(1H, d, J=8.2Hz), 6.74-7.37(6H, m)

Table D-149

Example 149

Phe(4-F)-N-Me-D-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH_2

R								
neoPent:D								
Reaction1								
Compound T4 (g)	Compound I12 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.990	0.980	0.90	30.00	12	nHx:EA=1:2	I-a149	1.250
Reaction2-a								
Compound I-a149(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.250	3.90	19.50	3	MC:MeOH=20:1		I-b149	0.99	
Reaction3								
Compound I-b149(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.970	0.780	0.71	50.00	5	nHx:EA=1:2	I-c149	1.500
Reaction4-b								
Compound I-c149(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.500	0.230	20.00	2	MC:MeOH=20:1		0.83	22.63	
ESI-MS(M^++1):557								
1H-NMR(CD_3OD):(two rotamer) δ 0.62 and 0.84(9H, s), 0.88 and 1.35(2H, s), 1.40(9H, s), 2.45 and 2.82(3H, s), 2.84-2.95(3H, m), 3.04 and 3.10(3H, s), 3.23(1H, dd, J=14.7, 4.9Hz), 4.65(1H, dd, J=8.0, 2.3Hz), 5.28(1H, m), 5.45(1H, dd, J=11.8, 5.1Hz), 6.63(1H, d, J=7.9Hz), 6.88(1H, dd, J=8.0, 2.3Hz), 7.01(2H, m), 7.10(1H, d, J=2.3Hz), 7.25(2H, dd, J=8.5, 5.4Hz)								

Table D-150A

Example 150A(less polar)

Phe(4-F)-*N*-Me-Ala(β-CF_3)-*N*-Me-Tyr(3-tBu)-NH_2

R
CH_2CF_3:L,D-mixture

Reaction1

Compound T4(g)	Compound I13(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.560	0.560	0.51	20.00	5.000	nHx:EA=1:1	I-a150	0.980

Reaction2-b

Compound I-a150(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.980	0.500	20.00	2	MC:MeOH =15:1	I-b150A	0.360(less polar)
					I-b150B	0.280(more polar)

Reaction3

Compound I-b150A(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.360	0.310	0.270	0.27	15.00	12	nHx:EA=1:1	I-c150A	0.32

Reaction4-b

Compound I-c150A(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.310	0.150	10.00	2	EA:MeOH =15:1	0.200	18.66

ESI-MS(M^++1): 569

1H-NMR(CD3OD):(two rotamers) δ 1.38 and 1.41(9H, s), 2.20, 2.56, 2.91, and 2.99(6H, s), 2.38-3.03(4H, m), 3.25 and 3.31(1H, d, J=4.8Hz), 3.72(1H, t, J=7.2Hz), 4.73(1H, brs), 5.53 and 5.57(1H, d, J=4.6Hz), 5.80(1H, q, J=4.4Hz), 6.55-6.79(2H, m), 7.00-7.15(3H, m), 7.25-7.30(2H, m)

Table D-150B

Example 150B(more polar)

Phe(4-F)-N-Me-Ala(β-CF_3)-N-Me-Tyr(3-tBu)-NH_2

R								
CH_2CF_3:L,D-mixture								
Reaction3								
Compound I-b150B(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.200	0.20	15.00	12.00	nHx:EA =1:1	I-c150B	0.300
Reaction4-b								
Compound I-c150B(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.300	0.150	10.00	2	EA:MeOH =20:1		0.170	21.51	
ESI-MS(M^++1): 569								
1H-NMR(CD_3OD):(two rotamers) δ 1.40(9H, s), 2.19-2.40(2H, m), 2.73 and 2.76(1H, d, J=7.0Hz), 2.89(3H, s), 2.92-2.96(1H, m), 2.98(3H, s), 3.21 and 3.24(1H, d, J=6.1Hz), 4.03(1H, t, J=7.2Hz), 4.52-4.61(1H, m), 5.36(1H, q, J=5.5Hz), 5.61(1H, t, J=7.0Hz), 6.67(1H, d, J=8.0Hz), 6.89(1H, dd, J=7.9, 2.4Hz), 7.01-7.10(3H, m), 7.24-7.29(2H, m)								

Table D-151

Example 151

Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH_2

R								
c-Hex								
Reaction1								
Compound T4 (g)	Compound I14(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.290	1.500	2.650	1.45	30.00	20	nHx:EA=1:1	I-a151	0.700
Reaction2-a								
Compound I-a151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.700	4.00	20.00	4	MC:MeOH =20:1		I-b151	0.400	
Reaction3								
Compound I-b151(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.380	0.760	0.41	20.00	20	nHx:EA=1:1	I-c151	0.500
Reaction4-a								
Compound I-c151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.500	4.00	20.00	4	MC:MeOH =20:1		0.400	20.140	
ESI-MS(M^++1): 569								
1H-NMR($CDCl_3$): (two rotamers) δ 0.72-1.68(10 H, m), 1.35 and 1.40(9H, s), 1.82-2.10(1H, m), 2.30-2.65(1H, m), 2.52(3H,s), 2.70-2.90(1H, m), 2.75(3H, s), 2.75-2.90(1H, m), 3.05-3.40(3H, m), 3.60-3.85(1H, m), 5.05-5.20(2H, m), 6.35-6.75(2H, m), 6.75-7.20(5H, m)								

Table D-152

Example 152

Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH_2

R
c-Hex:D

Reaction1

Compound T4 (g)	Compound I15(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.620	1.520	0.69	20.00	20	nHx:EA=1:1	I-a152	0.540

Reaction2-a

Compound I-a152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.540	3.00	15.00	4	MC:MeOH =20:1	I-b152	0.250

Reaction3

Compound I-b152(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.240	0.470	0.26	15.00	20	nHx:EA=1:1	I-c152	0.350

Reaction4-a

Compound I-c152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.350	3.00	10.00	4	MC:MeOH =20:1	0.27	22.040

ESI-MS(M^++1): 569

1H-NMR(CDCl3): (two rotamers) δ 0.65-1.70(11H, m), 1.38(9H, s), 2.15-2.35(1H, m), 2.25(3H, s), 2.75-3.05(1H, m), 2.95(3H, s), 3.10-3.25(3H, m), 5.20-5.27(2H, m), 5.55-5.65(1H, m), 6.15-6.25(2H, m), 6.54 and 6.57(2H, d, J=8.4 Hz), 6.75-6.95(1H, m), 7.05-7.15(2H, m)

Table D-153

Example 153

Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH_2

R
CH_2c-Hex

Reaction1

Compound T4 (g)	Compound I16 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.950	1.300	1.150	1.10	38.00	15	nHx:EA=1:1	I-a153	1.600

Reaction2-a

Compound I-a153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.600	4.80	24.00	3	MC:MeOH =20:1	I-b153	0.840

Reaction3

Compound I-b153 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.840	0.680	0.620	0.60	20.00	15	nHx:EA=1:1	I-c153	1.100

Reaction4-a

Compound I-c153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.100	2.40	12.00	3	MC:MeOH =30:1	0.50	21.154

ESI-MS(M^++1): 583

1H-NMR($CDCl_3$): (two rotamers) δ 0.09-1.88(13H, m), 1.35 and 1.26(9H, s), 2.32-2.80(2H, m), 2.46 and 2.74(3H, s), 2.83-3.27(3H, m), 2.99 and 3.03(3H, s), 3.59-3.73 and 3.81-3.95(1H, m), 4.62-4.74 and 5.11-5.25(1H, m), 5.27-5.59(2H, m), 6.08(1/2H, brs), 6.44 and 6.63(1H, d, J=7.9-8.3Hz), 6.77 and 6.87(1H, dd, J=7.2-7.5 1.8-1.9Hz), 6.92-7.20(5H, m), 7.59(1/2H, brs)

Table D-154

Example 154

Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH_2

R								
CH_2c-Hex:D								
Reaction1								
Compound T4 (g)	Compound I17 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	1.000	0.900	0.80	29.00	15	nHx:EA=1:1	I-a154	1.200
Reaction2-a								
Compound I-a154(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.200	3.60	18.00	3	MC:MeOH =20:1		I-b154	0.740	
Reaction3								
Compound I-b154(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.740	0.600	0.540	0.50	17.00	15	nHx:EA=1:1	I-c154	0.900
Reaction4-a								
Compound I-c154 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	2.00	10.00	3	MC:MeOH =30:1		0.24	25.144	
ESI-MS(M^++1): 583								
1H-NMR($CDCl_3$): δ 0.62-1.37(13H, m), 1.37(9H, m), 2.67-3.10(7H, m), 2.88(3H, s), 2.97(3H, s), 3.30 and 3.35(1H, d, J=3.3-3.4Hz), 3.95(1H, t, J=6.9Hz), 5.04 and 5.08(1H, d, J=4.2-4.5Hz), 5.43 and 5.47(1H, d, J=5.4-5.8Hz), 5.52(1H, brs), 6.37(1H, brs), 6.58(1H, d, J=7.9Hz), 6.79-7.09(4H, m), 7.11(1H, d, J=5.2Hz), 7.14(1H, d, J=5.4Hz)								

Table D-155

Example 155

Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH_2

R
CH_2Ph

Reaction1

Compound T4 (g)	Compound I18 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	1.000	1.230	0.89	20.00	20	nHx:EA =1:1	I-a155	1.390

Reaction2-b

Compound I-a155(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.390	0.300	20.00	20	MC:MeOH =20:1	I-b155	0.840

Reaction3

Compound I-b155(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	15.00	20	nHx:EA =1:1	I-c155	0.997

Reaction4-a

Compound I-c155(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.997	3.00	10.00	4	MC:MeOH =20:1	0.68	19.710

ESI-MS(M^++1): 577

1H-NMR($CDCl_3$):(two rotamers) δ 1.40 and 1.42(9H, s), 2.54(3H, s), 2.61-3.04(5H, m), 3.15-3.39(4H, m), 3.67-3.85(1H, m), 5.32-5.72(2H, m), 6.57-6.72(1H, m), 6.98-7.29(10H, m)

Table D-156

Example 156

Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH_2

R
CH_2Ph:D

Reaction1

Compound T4 (g)	Compound I19 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.800	1.230	0.89	20.00	20	nHx:EA=1:1	I-a156	1.140

Reaction2-a

Compound I-a156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.140	3.00	10.00	4	MC:MeOH =20:1	I-b156	0.990

Reaction3

Compound I-b156(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	20.00	20	nHx:EA=1:1	I-c156	0.960

Reaction4-a

Compound I-c156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.960	3.00	10.00	4	MC:MeOH =20:1	0.73	21.960

ESI-MS(M^++1): 577

1H-NMR($CDCl_3$): δ 1.42(9H, s), 2.47-2.65(4H, m), 2.97-3.25(2H, m), 3.04(3H,s), 3.15(3H, s), 3.32-3.51(3H, m), 4.01-4.15(1H, m), 6.75-6.80(1H, m), 6.82-7.45(1H, m)

Table D-157

Example 157

Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2

R								
CH_2Phe(4-F)								
Reaction1								
Compound T4 (g)	Compound I20 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.960	1.370	1.180	1.10	38.00	15	nHx:EA=1:2	I-a157	1.880
Reaction2-a								
Compound I-a157 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.880	5.40	27.00	3	MC:MeOH =20:1		I-b157	1.220	
Reaction3								
Compound I-b157(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.220	0.780	0.710	0.60	23.00	18	nHx:EA=1:2	I-c157	1.550
Reaction4-a								
Compound I-c157 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.550	3.30	16.00	3	MC:MeOH =20:1		0.73	21.035	
ESI-MS(M^++1): 595								
1H-NMR($CDCl_3$): (two rotamers) δ 1.28 and 1.35(9H, s), 2.30-3.25(12H, m), 2.38 and 2.56(3H, s), 2.86 and 2.99(3H, s), 3.49-3.72(1H, m), 4.84-5.17(1H, m), 5.18-5.41(2H, m), 5.51-5.78(1H, m), 6.38 and 6.43(1H, d, J=8.3Hz), 6.60-7.23(10H, m)								

Table D-158

Example 158

Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH_2

R
CH_2Phe(4-F):D

Reaction1

Compound T4 (g)	Compound I21 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.000	0.850	0.80	27.00	18	nHx:EA=1:2	I-a158	1.120

Reaction2-a

Compound I-a158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.120	3.30	16.50	3	MC:MeOH =20:1	I-b158	0.880

Reaction3

Compound I-b158 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.880	0.560	0.500	0.50	16.00	15	nHx:EA=1:2	I-c158	0.900

Reaction4-a

Compound I-c158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.900	2.00	10.00	3	MC:MeOH =20:1	0.30	23.049

ESI-MS(M^++1): 595

1H-NMR($CDCl_3$): (two rotamers) d 1.34 and 1.37(9H, s), 2.38-2.51(1H, m), 2.53-2.82(5H, m), 2.86(3H, s), 2.88(3H, s), 3.04-3.15(1H, m), 3.21 and 3.26(1H, d, J=6.4-6.3), 3.78-3.95(1H, m), 5.26-5.38(1H, m), 5.38-5.52(1H, m), 5.62(1H, brs), 6.27(1H, brs), 6.79(1H, d, J=8.1Hz), 6.78(1H, d, J=8.7Hz), 6.83-7.22(9H, m)

Table D-159

Example 159

Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2

R
$CH_2Ph(4\text{-}Cl)$

Reaction1

Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.080	1.630	1.330	0.91	20.00	16	nHx:EA=1:1	I-a159	2.000

Reaction2-a

Compound I-a159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	5.60	25.00	1	MC:MeOH =20:1	I-b159	1.13

Reaction3

Compound I-b159 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.861	0.777	0.53	20.00	3	nHx:EA=1:1	I-c159	0.908

Reaction4-a

Compound I-c159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.908	1.96	10.00	3	MC:MeOH =20:1	0.625	21.59

ESI-MS(M^++1):612

1H-NMR($CDCl_3$): (two rotamers) d 1.28 and 1.35(9H,s), 2.38 and 2.55(3H, s), 2.40-3.32(6H, m), 2.85 and 3.0(3H, s), 3.56 and 3.72(1H, t, J = 8.8Hz), 4.92(2/5H, m), 5.20-5.50(5/2H, m), 5.60 and 5.78(3/5H, brs), 6.35-7.40(25/2H, m)

Table D-160

Example 160

Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH_2

R
$CH_2Ph(4\text{-}Cl)$:D

Reaction1

Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.519	0.781	0.639	0.44	10.00	16	nHx:EA=1:1	I-a160	0.947

Reaction2-a

Compound I-a160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.947	5.60	15.00	1	MC:MeOH =20:1	I-b160	0.624

Reaction3

Compound I-b160 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.476	0.430	0.30	15.00	3	nHx:EA=1:1	I-c160	0.46

Reaction4-a

Compound I-c160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.460	1.00	5.00	3	MC:MeOH =20:1	0.300	19.53

ESI-MS(M^++1):612

1H-NMR($CDCl_3$): d 1.35(9H,s), 1.30-2.96(5H, m), 2.88(3H, s), 2.89(3H, s), 3.03-3.35(1H, m), 3.83(3/4H, m), 5.29(2H, s), 5.43(6/4H, m), 6.20(3/4H, brs), 6.52(1H, d, J=8.8Hz), 6.78(1H, d, J=8.8Hz), 6.90-7.32(10H, m)

Table D-161

Example 161

Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH_2

R
$CH_2Ph(4\text{-}OH)$

Reaction1

Compound T4 (g)	Compound I24 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	2.600	1.730	1.09	30.00	3	nHx:EA=1:1	I-a161	2.610

Reaction2-a

Compound I-a161(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.610	6.47	33.00	3	MC:MeOH =20:1	I-b161	1.300

Reaction3

Compound I-b161 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.200	0.964	0.70	30.00	3	nHx:EA=1:1	I-c161	1.880

Reaction4-b

Compound I-c161(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.880	0.282	40.00	3	MC:MeOH =20:1	0.500	17.94

ESI-MS(M^++1):593

1H-NMR(CD_3OD): (two rotamers) d 1.41 and 1.42(9H,s), 2.32 and 2.39(3H, s), 2.90 and 3.07(3H, s), 2.59-3.50(7H, m), 3.72 and 3.85(1/2H, m), 5.05 and 5.30(1/2H, m), 5.60(1H, m), 6.50-7.43(11H, m)

Table D-162

Example 162

Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH_2

R
$CH_2Ph(4\text{-}OH)$:D

Reaction1

Compound T4 (g)	Compound I25 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	2.000	1.220	0.77	30.00	3	nHx:EA=1:1	I-a162	1.550

Reaction2-b

Compound I-a162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.550	0.233	20.00	12	MC:MeOH =20:1	I-b162	0.977

Reaction3

Compound I-b162 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.977	1.080	0.871	0.64	20.00	3	nHx:EA=1:1	I-c162	1.330

Reaction4-b

Compound I-c162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
1.330	0.200	30.00	3	MC:MeOH =20:1	0.500	18.54

ESI-MS(M^++1):593

1H-NMR(CD_3OD): δ 1.45(9H,s), 2.42-2.75(4H, m), 3.02(3H, s), 2.34-3.15(2H, m), 3.32(1/5H, dd, J =7.6, 8.8Hz), 4.03(4/5H, t, J=8.8Hz), 5.42-5.65(2H, m), 6.65-7.25(12H, m)

Table D-163

Example 163

Phe(4-F)-N-Me-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2

R								
CH_2(2-Thienyl)								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.670	0.916	0.820	0.56	20.00	16	nHx:EA=1:1	I-a163	1.280
Reaction2-a								
Compound I-a163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.280	3.80	19.00	3	MC:MeOH =20:1		I-b163	0.513	
Reaction3								
Compound I-b163 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.418	0.379	0.30	20.00	3	nHx:EA=1:1	I-c163	0.587
Reaction4-a								
Compound I-c163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.587	1.32	10.00	3	MC:MeOH =20:1		0.35	23.7	
ESI-MS(M^++1):583								
1H-NMR($CDCl_3$+ CD_3OD): (two rotamers) δ 1.30 and 1.35(9H,s), 1.80(1/3H, m), 2.25, 2.58 and 2.88, 3.0(6H, s), 2.0-3.25(5H, m), 3.35(2/3H, m), 3.60(1H, m), 4.90(1/3H, m), 5.27(2/3H, m), 5.37-5.64(1H, m), 6.40-6.72(2H, m), 6.72-7.20(8H, m)								

Table D-164

Example 164

Phe(4-F)-N-Me-D-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH_2

R								
CH_2(2-Thienyl):D								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.040	0.930	0.64	20.00	16	nHx:EA=1:1	I-a164	1.430
Reaction2-a								
Compound I-a164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.430	4.43	25.00	3	MC:MeOH =20:1		I-b164	0.500	
Reaction3								
Compound I-b164 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.400	0.360	0.28	20.00	3	nHx:EA=1:1	I-c164	0.857
Reaction4-a								
Compound I-c164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.857	1.92	15.00	3	MC:MeOH =20:1		0.33	21.7	
ESI-MS(M^++1):583								
1H-NMR($CDCl_3$): δ 1.35(9H,s), 2.17-3.20(7H, m), 2.91(3H, s), 2.95(3H, s), 3.28(1/2H, dd, J=15.8, 7.9Hz), 3.85(1/2H, t, J=7.9Hz), 5.35 and 5.45(2H, m), 5.65(1H, brs), 6.28(2/3H, brs), 6.48-7.30(28/3H, m)								

Table D-165

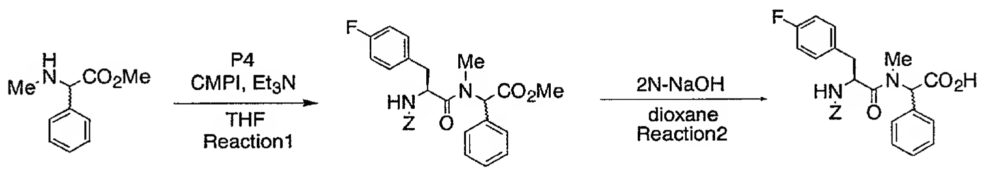
Example 165

Phe(4-F)-N-Me-Ala(β-c-Pr)-N-Me-Tyr(3-tBu)-NH_2

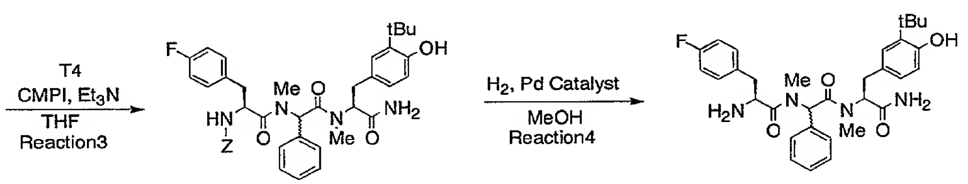
R								
CH_2c-Pr								
Reaction1								
Compound T4 (g)	Compound I28 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.820	1.100	1.000	0.90	33.00	17	nHx:EA=1:1	I-a165	1.260
Reaction2-b								
Compound I-a165 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.260	0.120	24.00	3	MC:MeOH =30:1		I-b165	0.600	
Reaction3								
Compound I-b165 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.540	0.490	0.50	16.00	18	nHx:EA=1:1	I-c165	0.590
Reaction4-a								
Compound I-c165 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.590	1.40	7.00	3	MC:MeOH =30:1		0.300	18.61	
ESI-MS(M^++1): 541								
1H-NMR(CD_3OD): (two rotamers) δ 0.85-0.78(5H, m), 1.39-1.91(2H, m), 1.47 and 1.49(9H, s), 2.34 and 2.69(3H, s), 2.49-3.38(4H, m), 2.98 and 3.03(3H, s), 3.75-3.48(1H, m), 5.06-5.15 and 5.49-5.67(2H, m), 6.65-6.88(2H, m), 7.04-7.43(5H, m)								

Scheme 10 shows the synthesis process of Examples 166 and 176.

Scheme 10: Synthesis process of Examples 166 and 176



I29, I30 I-a166, I-a176 I-b166, I-b176



I-c166, I-c176

The synthesis process in scheme 10 is explained below.

Reaction step 1)

To solutions of Compound P4, Compounds I29 and I30 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a166 and I-a176.

Reaction step 2)

To solutions of Compounds I-a166 and I-a176 in

dioxane, 2N NaOH was added and stirred at room temperature. The reaction mixtures were adjusted to pH 3 to 4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b166 and I-b176.

Reaction step 3)

To solutions of Compounds I-b166 and I-b176, Compound T4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c166 and I-c176.

Reaction step 4)

To solutions of Compounds I-c166 and I-c176 in methanol, $Pd(OH)_2$ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the $Pd(OH)_2$, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Examples conducted according to Scheme 10 are shown in Tables D-166 and D-176.

Table D-166

Example 166

Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH_2

Reaction1

Compound I29 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	1.000	1.170	1.22	30.00	3	nHx:EA =1:1	I-a166	1.070

Reaction2

Compound I-a166(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.070	2.50	20.00	3	MC:MeOH =20:1	I-b166	1.030

Reaction3

Compound I-b166 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.030	0.504	0.668	0.42	20.00	3	nHx:EA =1:1	I-c166	0.595

Reaction4

Compound I-c166(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.595	0.100	10.00	3	MC:MeOH =20:1	0.480	20.00

ESI-MS(M^++1):563

1H-NMR(CD_3OD): (two rotamers) δ 1.40 and 1.49(9H,s), 2.75 and 2.90(3H, s), 2.95 and 3.15(3H, s), 2.53-3.50(5H, m) 4.12(1H, m), 4.74 and 5.32(1H, m), 6.40-7.58(15H, m)

Table D-176

Example 176

Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH_2

Reaction1								
Compound I30 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.646	2.160	2.300	1.45	20.00	3	nHx:EA =1:1	I-a176	1.030

Reaction2						
Compound I-a176(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.030	2.40	20.00	3	MC:MeOH =20:1	I-b176	0.540

Reaction3								
Compound I-b176 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.540	0.268	0.355	0.22	10.00	3	nHx:EA =1:1	I-c176	0.450

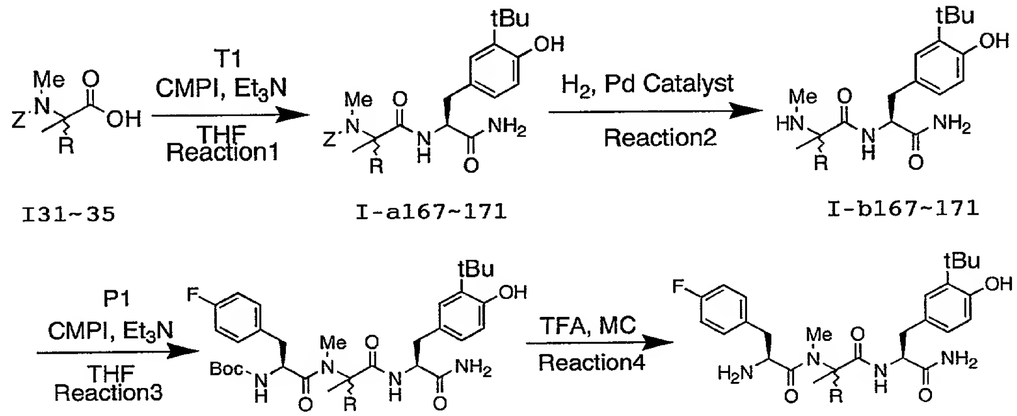
Reaction4						
Compound I-c176(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.450	0.070	10.00	3	MC:MeOH =20:1	0.270	20.98

ESI-MS(M^++1):563

1H-NMR(CD_3OD): δ 1.46(9H,s), 2.50(3H, s), 2.82(3H, s), 2.72-3.13(3H, m), 3.402H, m), 4.20(1H, m), 5.48(1H, dd, J=13.2, 6.2Hz), 6.25(1H, brs), 6.35(2H, d, J=8.8Hz), 6.75(1H, d, J=8.8Hz), 6.90(1H, dd, J=8.8, 1.7Hz), 7.05-7.45(8H, m)

Scheme 11 shows the synthesis process of Examples 167-171.

Scheme 11: Synthesis scheme of Examples 167-171



I31~35 I-a167~171 I-b167~171

I-c167~171

The synthesis process in scheme 11 is explained below.

Reaction step 1)

To solutions of Compound T1, Compounds I31 to I35 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a167 to I-a171.

Reaction step 2)

To solutions of Compounds I-a167 to I-a171 in methanol, Pd/C was added and stirred in a hydrogen

atmosphere at room temperature. After filtering off the Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b167 to I-b171.

Reaction step 3)

To solutions of Compounds I-b167 to I-b171, Compound P1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c167 to I-c171.

Reaction step 4)

To solutions of Compounds I-c167 to I-c171 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated $NaHCO_3$ aqueous solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Examples conducted according to Scheme 11 are shown in Tables D-167 to D-171.

Table D-167

Example 167

Phe(4-F)-N-Me-α-Me-Phe-Tyr(3-tBu)-NH_2

R								
CH_2Phe								
Reaction1								
Compound T1 (g)	Compound I31 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.570	1.180	0.900	0.80	24.00	5	nHx:EA =1:2	I-a167	0.360
Reaction2								
Compound I-a167 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.360	0.040	6.00	3		I-b167		0.260	
Reaction3								
Compound I-b167 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.260	0.420	0.780	0.40	6.30	120	nHx:EA =1:2	I-c167	0.060
Reaction4								
Compound I-c167 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.060	0.20	0.70	3	MC:MeOH =20:1		0.01	21.813	
ESI-MS(M^++1): 577								
1H-NMR($CDCl_3$): δ 1.30(3H, s), 1.34(9H, s), 2.37-2.62(3H, m), 2.51(3H, s), 3.07(1H, d, J=14.5Hz), 3.24-3.41(2H, m), 3.73(1H, t, J=8.3Hz), 4.48-4.57(1H, m), 5.37-5.58(2H, m), 6.50(1H, d, J=9.0Hz), 6.75(1H, d, J=9.3Hz), 6.77(1H, s), 6.97-7.37(9H, m)								

Table D-168

Example 168

Phe(4-F)-N-Me-α-Me-Phe-Tyr(3-tBu)-NH_2:Diastereomeric mixture

R
CH_2Phe:D

Reaction1

Compound T1 (g)	Compound I32 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.390	0.820	0.640	0.60	16.00	5	nHx:EA =1:2	I-a168	0.670

Reaction2

Compound I-a168 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
0.670	0.060	12.00	3	I-b168	0.500

Reaction3

Compound I-b168 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.810	1.400	1.20	12.00	120	nHx:EA =2:1	I-c168	0.210

Reaction4

Compound I-c168 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.210	0.53	2.60	3	MC:MeOH =20:1	0.070	20.15/20.93

ESI-MS(M^++1): 577

1H-NMR($CDCl_3$): (two rotamers) δ 1.12-1.41(3H, m), 1.35(9H, s), 1.98 and 2.40(3H, s), 2.36(1H, s), 2.46-2.78(2H, m), 2.82-3.28(4H, m), 3.42-3.83(2H, m), 4.52-4.72(1H, m), 5.38-5.56(1H, m), 5.98-6.22(1H, m), 6.61-6.28(2H, m), 6.35-7.38(10H, m)

Table D-169

Example 169

Phe(4-F)-N-Me-α-Me-Leu-Tyr(3-tBu)-NH_2

R
i-Bu

Reaction1

Compound T1 (g)	Compound I33 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.560	1.770	2.310	1.68	60.00	12	nHx:EA:MC = 1:1.5:1	I-a169	2.390

Reaction2

Compound I-a169(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
2.390	0.360	80.00	12	I-b169	1.490

Reaction3

Compound I-b169(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.490	1.230	1.510	1.10	78.00	12	nHx:EA=1:2	I-c169	0.910

Reaction4-a

Compound I-c169(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.850	1.30	1.30	4	MC:MeOH =25:1	0.130	21.50

ESI-MS(M^++1):543

1H-NMR(CD_3OD): δ 0.79(6H, t, J=7.0Hz), 1.27(3H, s), 1.46(9H, s), 1.51-1.79(3H, m), 2.54-2.67(2H, m), 2.76(3H, s), 3.04(1H, dd, J=14.3, 5.6Hz), 3.21(1H, dd, J=14.0, 6.8Hz), 3.81(1H, t, J=6.5-7.1Hz), 4.56(1H, dd, J=14.1, 6.4Hz), 5.39(1H, brs), 5.78(1H, brs), 6.61(1H, d, J=7.8Hz), 6.93-7.14(6H, m), 7.45(1H, brs)

Table D-170

Example 170

Phe(4-F)-N-Me-α-Me-D-Abu-Tyr(3-tBu)-NH_2

R
Et:D

Reaction1

Compound T1(g)	Compound I34(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.147	0.150	0.220	0.16	3.00	12	nHx:EA =1:1	I-a170	0.251

Reaction2

Compound I-a170(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
0.250	0.150	5.00	3	I-b170	0.151

Reaction3

Compound I-b170(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.150	0.18	0.160	0.12	3.00	16	nHx:EA =1:1	I-c170	0.145

Reaction4

Compound I-c170(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.140	0.60	3.00	2.5	EA:MeOH =20:1	0.075	19.5

ESI-MS(M^++1):515

1H-NMR($CDCl_3$): δ 0.57(3H, t, J=7.6Hz), 1.21(3H, s), 1.37(9H, s), 1.63-1.82(2H, m), 1.70-1.92(2H, m), 2.59-2.71(2H, m), 2.72(3H, s), 3.03-3.21(2H, m), 3.84(1H, t, J=7.0Hz), 4.60(1H, q, J=6.0Hz), 5.51(1H, brs), 5.84(1H, d, J=7.3 Hz), 6.62(1H, d, J=8.0Hz), 6.91-7.03(5H, m), 7.09-7.14(2H, m), 7.54(1H, s)

Table D-171

Example 171

Phe(4-F)-N-Me-α-Me-D-Val-Tyr(3-tBu)-NH_2

R
i-Pr:D

Reaction1

Compound T1 (g)	Compound I35 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.144	0.170	0.150	0.17	3.6	12	nHx:EA=3:2	I-a171	0.120

Reaction2

Compound I-a171(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
0.120	0.020	5.00	1.5	I-b171	0.080

Reaction3

Compound I-b171(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.080	0.190	0.170	0.12	2.00	30	nHx:EA=2:3	I-c171	0.050

Reaction4

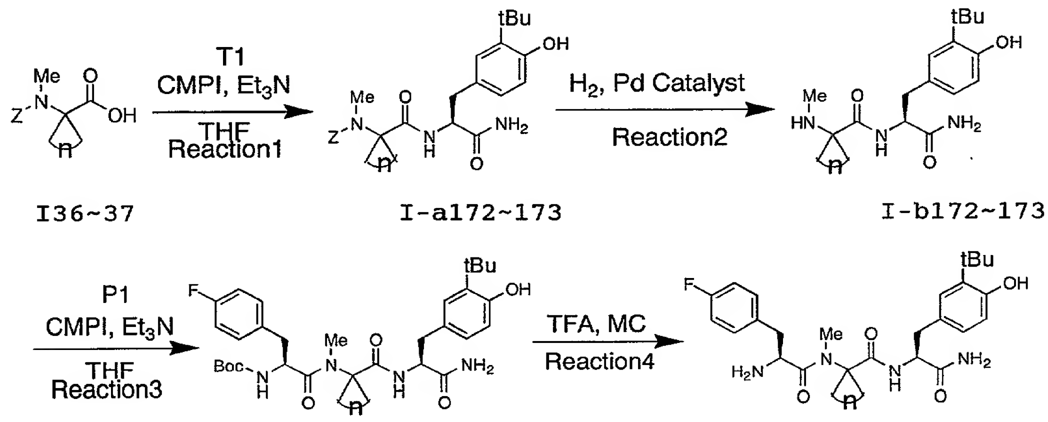
Compound I-c171(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.050	0.36	1.00	3	MC:MeOH =7:1	0.02	20.40

ESI-MS(M^++1):529

1H-NMR($CDCl_3$): δ 0.69(3H, d, J=6.7Hz), 0.85(3H, d, J=6.7Hz), 1.16(3H, s), 1.36(9H, s), 1.76-1.92(1H, m), 2.27-2.44(1H, m), 2.52-2.70(2H, m), 2.82(3H, s), 3.03-3.24(2H, m), 4.54-4.62(1H, m), 5..47(1H, brs), 5.76(1H, d, J=7.5Hz), 6.60(1H, d, J=8.1Hz), 6.87-7.06(4H, m), 7.09-7.16(2H, m), 7.37(1H, brs)

Scheme 12 shows the synthesis process of Examples 172 and 173.

Scheme 12: Synthesis scheme of Examples 172 and 173



I36~37 I-a172~173 I-b172~173

I-c172~173

The synthesis process in scheme 12 is explained below.

Reaction step 1)

To solutions of Compound T1, Compounds I36 and I37 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a172 and I-173.

Reaction step 2)

To solutions of Compounds I-a172 and I-a173 in methanol, $Pd(OH)_2$ was added and stirred in a hydrogen

atmosphere at room temperature. After filtering off the $Pd(OH)_2$, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b172 and I-b173.

Reaction step 3)

To solutions of Compounds I-b172 and I-b173, Compound P1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c172 and I-c173.

(Reaction step 4)

To solutions of Compounds I-c172 and I-c173 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Examples conducted according to Scheme 12 are shown in Tables D-172 and D-173.

Table D-172

Example 172

(2S)-N-[(N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

Reaction1

Compound T1 (g)	Compound 136 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	1.050	0.973	0.70	20.00	3	nHx:EA =1:1	I-a172	1.210

Reaction2

Compound I-a172(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Product	Column sol.
1.210	0.182	30.00	3	I-b172	MC:MeOH =20:1

Reaction3

Compound I-b172 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.744	1.170	1.050	0.72	20.00	52	nHx:EA =1:1	I-c172	0.518

Reaction4

Compound I-c172(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.518	1.330	10.00	3	MC:MeOH =20:1	0.130	19.59

ESI-MS(M^{+}+1):527

1H-NMR($CDCl_3$): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.42(8H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m),4.30 and 4.61(1H, m), 5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)

Table D-173

Example 173

(2S)-N-[(N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

Reaction1

Compound T1(g)	Compound I37 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.708	1.310	0.766	0.84	20.00	3	nHx:EA =1:1	I-a173	1.400

Reaction2

Compound I-a173(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
1.400	0.210	30.00	3	I-b173	0.934

Reaction3

Compound I-b173 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.930	1.410	1.270	0.87	30.00	120	nHx:EA =1:1	I-c173	0.271

Reaction4

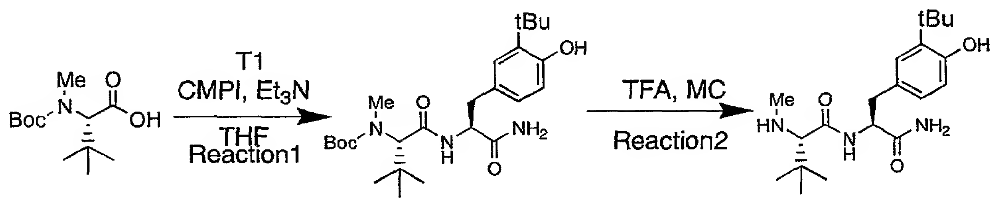
Compound I-c173(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.271	0.700	5.00	3	MC:MeOH =20:1	0.030	24.76

ESI-MS(M^{+}+1):541

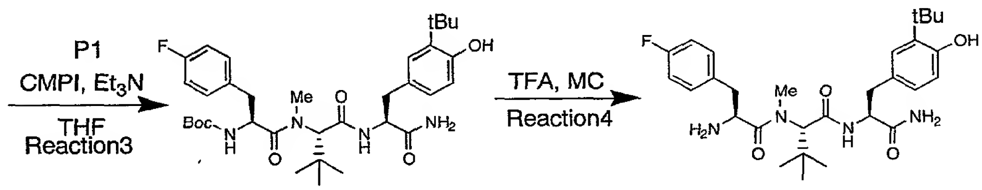
1H-NMR($CDCl_3$): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.50(10H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m), 4.30 and 4.61(1H, m),5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)

Scheme 13 shows the synthesis process of Example 174.

Scheme 13: Synthesis scheme of Example 174



I38 I-a174 I-b174



I-c174 Compound of Example 174

The synthesis process in scheme 13 is explained below.

Reaction step 1)

To a solution of Compound T1, Compound I38 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a174.

Reaction step 2)

To a solution of Compound I-a174 in dichloromethane, TFA was added under cooling and stirred at room temperature.

The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b174.

(Reaction step 3)

To a solution of Compound I-b174, Compound P1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c174.

(Reaction step 4)

To a solution of Compound I-c174 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Example conducted according to Scheme 13 is shown in Table D-174.

Table D-174

Example 174

Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH_2

Reaction1

Compound T1 (g)	Compound I38 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.633	0.660	0.756	0.37	15.00	24	nHx:EA =1:2	I-a174	0.670

Reaction2

Compound I-a174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.670	2.00	10.00	1	MC:MeOH =10:1	I-b174	0.518

Reaction3

Compound I-b174(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.518	0.809	0.730	0.40	10.00	36	nHx:EA =1:2	I-c174	0.393

Reaction4

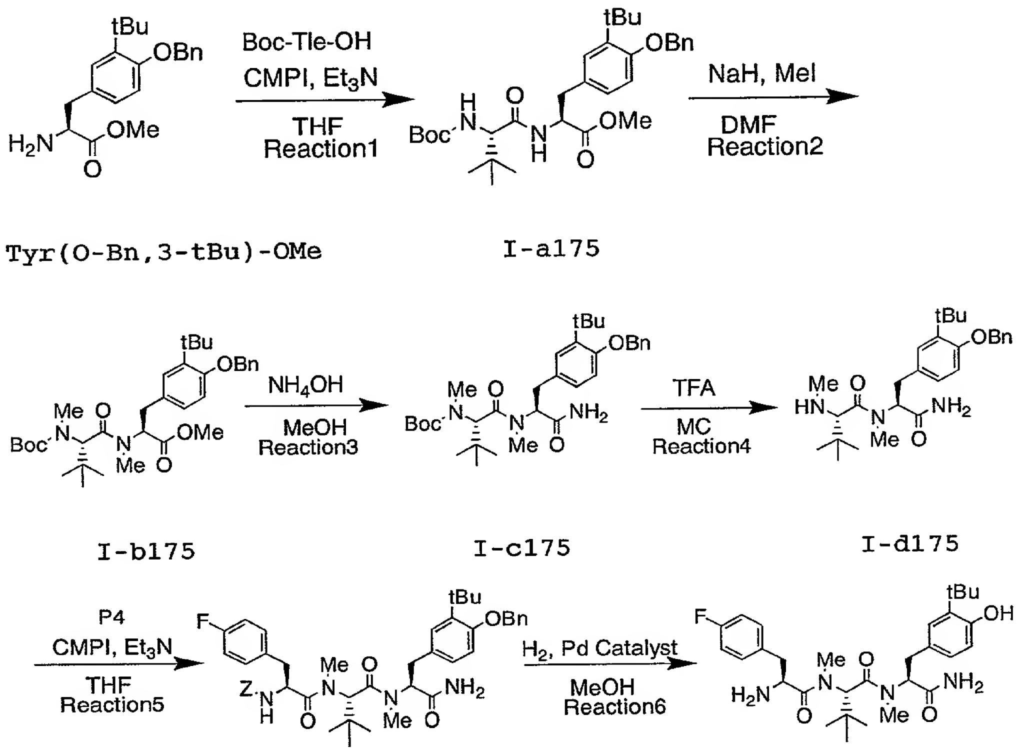
Compound I-c174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.393	1.00	5.00	1	MC:MeOH =15:1	0.162	17.54

ESI-MS(M^++1):529

1H-NMR($CDCl_3$):(two rotamers) δ 1.02 and 1.03 (9H,s), 1.35 and 1.36(9H, s), 2.75(3H, s), 2.70 and 3.00(4H, m), 3.12(1H, dd, J=10.3, 6.3Hz), 3.60 and 3.82(1H, m), 4.64(1H, m), 5.50(1H, brs), 5.80 and 6.00(1H, brs), 6.70(1H, s), 6.80-7.15(6H, m)

Scheme 14 shows the synthesis process of Example 175.

Scheme 14: Synthesis scheme of Example 175



Tyr(O-Bn,3-tBu)-OMe I-a175

I-b175 I-c175 I-d175

I-e175 Example 175

The synthesis process in scheme 14 is explained below.

Reaction step 1)

To a solution of Tyr(O-Bn,3-tBu)-OMe, Compound Boc-Tle-OH and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced

pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a175.

Reaction step 2)

To a solution of Compound I-a175 in DMF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixture was mixed with water under cooling, neutralized by the addition of 1N HCl and extracted with EA/nHx (1/2). The organic layer was washed three times with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b175.

Reaction step 3)

To a solution of Compound I-b175 in methanol, 28% aqueous ammonia was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c175.

Reaction step 4)

To a solution of Compound I-c175 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced

pressure, neutralized by the addition of a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-d175.

Reaction step 5)

To a solution of Compound I-d175, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-e175.

Reaction step 6)

To a solution of Compound I-e175 in methanol, $Pd(OH)_2$ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the $Pd(OH)_2$, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Example conducted according to Scheme 14 is shown in Table D-175.

Table D-175

Example 175

Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH_2

Reaction1

Tyr(O-Bn,3-tBu)-OMe (g)	Boc-Tle-OH (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.720	1.280	1.410	1.40	34.00	12	nHx:EA=5:1	I-a175	2.200

Reaction2

Compound I-a175 (g)	NaH (g)	Methyl Iodide(ml)	DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.200	0.480	2.22	22.00	1	nHx:EA=5:1	I-b175	1.930

Reaction3

Compound I-b175 (g)	NH_4OH (ml)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.930	130.00	230.00	20	nHx:EA=2:1	I-c175	0.564

Reaction4

Compound I-c175 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.680	2.78	8.00	1.5	MC:MeOH =20:1	I-d175	0.500

Reaction5

Compound I-d175 (g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.951	0.546	0.50	12.50	12	nHx:EA=2:1	I-d175	0.254

Reaction6

Compound I-d175 (g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.250	0.050	10.00	3	MC:MeOH =15:1	0.098	19.280

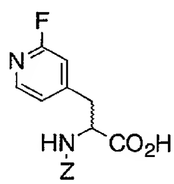
ESI-MS(M^++1):543

1H-NMR($CDCl_3$): δ 0.80(9H, s), 1.37(9H, s), 2.68(1H, dd, J=13.6, 7.3Hz), 2.85-3.01(2H, m), 2.92(3H, s), 2.98(3H, s), 3.11-3.22(1H, m), 3.94(1H, t, J=7.0Hz), 5.19(1H, s), 5.22(1H, brs), 5.37(1H, dd, J=10.5, 5.6Hz), 5.98(1H, brs), 6.55(1H, d, J=7.9Hz),6.88(1H, dd, J=8.0, 2.2Hz),6.94-7.00(2H, m),7.07-7.14(3H, m)

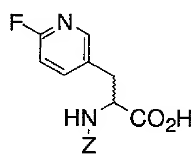
Methods of producing Intermediates in the scheme 15 are shown as Reference Examples in the following. The structural formulae of Intermediates of Examples 177-180 are shown in Table C-5.

Table C-5

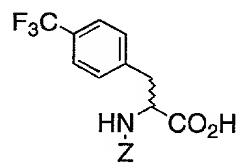
Intermediates of Examples 177-180



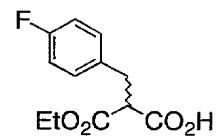
P6



P7



P8



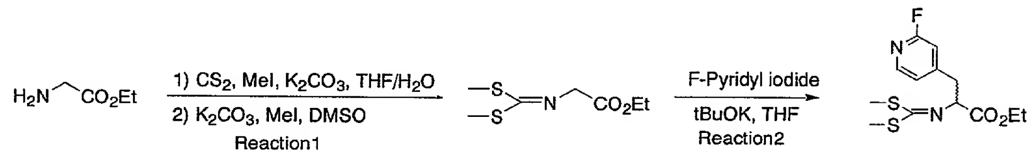
P9

Reference Example 27

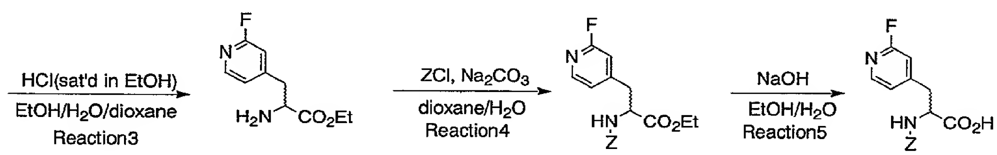
Synthesis of Intermediates P6-P8

The synthesis scheme is shown below.

Synthesis scheme of Intermediates P6-P8



Glycine ethyl ester hydrochloride | I-a177-I | I-b177-I



I-c177-I | I-d177-I | P6

The synthesis methods of Intermediates P6-P8 are explained below.

F-Pyridyl iodide [2-fluoro-4-(iodomethyl)pyridine and 2-fluoro-5-(iodomethyl)pyridine] were synthesized referring to J. Med. Chem., 1998, 41(23), 4615. P7 and P8 were synthesized according to a similar method of synthesizing P6 using the above 2-fluoro-5-(iodomethyl)pyridine and 4-(iodomethyl)-1-(trifluoromethyl)benzene.

Reaction step 1)

To a solution of glycine ethyl ester hydrochloride, CS_2 and water in THF, K_2CO_3 and CH_3I were added dropwise and

then stirred at room temperature. After the completion of the reaction, the reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; to a solution of the thus obtained residue in a mixture of DMSO and water, K_2CO_3 was added dropwise gradually and then under cooling with ice, CH_3I was added dropwise gradually, followed by stirring at room temperature. The reaction mixture was mixed with water, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a177-I.

Reaction step 2)

To a solution of Compound I-a177-I and t-BuOK in THF, F-pyridyl iodide was added dropwise gradually at -78°C while stirring. The reaction mixture was mixed with water, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b177-I.

Reaction step 3)

To a solution of Compound I-b177-I in a mixture of

ethanol, water and dioxane, a saturated HCl/ethanol solution was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c177-I.

Reaction step 4)

To a solution of Compound I-c177-I and Na_2CO_3 in a mixture of dioxane and water, Z-Cl was added dropwise gradually under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-d177-I.

Reaction step 5)

To a solution of Compound I-d177-I in dioxane, 2N NaOH was added and stirred at room temperature. The reaction mixture was adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column

chromatography (silica gel) to give Intermediate P6.

The results are shown in Tables E-46 to E-48.

Table E-46

Intermediate P6

3-(2-fluoro-4-pyridyl)-2-[(phenylmethoxy)carbonylamino]propanoic acid

Reaction1-a							
Gly-OEt HCl(g)	K_2CO_3 (g)	Methyl iodide(ml)	CS_2 (ml)	THF/H_2O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate (g)	K_2CO_3 (g)	Methyl iodide(ml)	DMSO/ H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA =5:1	I-a177-I	11.7000
Reaction2							
I-a177-I (g)	2-fluoro-4-(iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	2.520	1.190	32.00	2.50	nHx:EA =7:1	I-b177-I	2.480
Reaction3							
I-b177-I (g)	HCl(sat'd in EtOH) (ml)		EtOH/H_2O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
2.480	11.50		11.50 / 11.50	6	16	I-c177-I	1.33
Reaction4							
I-c177-I (g)	ZCl (ml)	Na_2CO_3 (g)	Dioxane/ H_2O (ml)		Reaction time (hr)	Product	Amount (g)
1.330	0.99	1.000	18.00 / 18.00		2	I-d177-I	1.36
Reaction5							
I-d177-I (g)	NaOH (g)	EtOH/H_2O (ml)		Reaction time (hr)		Amount (g)	
1.330	0.314	30.00 / 10.00		1.500		1.200	

Table E-47

Intermediate P7

3-(2-fluoro-5-pyridyl)-2-

[(phenylmethoxy)carbonylamino]propanoic acid

Reaction1-a

Gly-OEt HCl(g)	K_2CO_3 (g)	Methyl iodide(ml)	CS_2 (ml)	THF/H_2O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061

Reaction1-b

Crude intermediate(g)	K_2CO_3 (g)	Methyl iodide(ml)	DMSO/ H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA	I-a178-I	11.7000

Reaction2

I-a178-I (g)	2-fluoro-5-(iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.990	8.37	2.380	60.00	3.00	nHx:EA	I-b178-I	4.300

Reaction3

I-b178-I (g)	HCl(sat'd in EtOH)(ml)	EtOH/H_2O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
4.300	20.00	12.00 / 12.00	10.00	16	I-c178-I	1.880

Reaction4

I-c178-I (g)	ZCl (ml)	Na_2CO_3 (g)	Dioxane/ H2O (ml)	Reaction time (hr)	Product	Amount (g)
1.880	1.40	1.410	25.00 / 25.00	2	I-d178-I	2.940

Reaction5

I-d178-I (g)	NaOH (g)	EtOH/H_2O (ml)	Reaction time (hr)	Amount (g)
2.620	0.606	40.00 / 10.00	1.500	2.400

Table E-48

Intermediate P8

2-[(Phenylmethoxy)carbonylamino]-3-[4-(trifluoromethyl)phenyl]propanoic acid

Reaction1-a

Gly-OEt-HCl(g)	K_2CO_3 (g)	Methyl iodide(ml)	CS_2 (ml)	THF/H_2O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061

Reaction1-b

Crude intermediate(g)	K_2CO_3 (g)	Methyl iodide(ml)	DMSO/ H_2O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA =5:1	I-a179-I	11.700

Reaction2

I-a179-I (g)	4-(iodomethyl)-1-(trifluoro methyl)benzene (ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.120	3.220	1.270	40.00	2	nHx:EA =7:1	I-b179-I	3.730

Reaction3

I-b179-I (g)	HCl (sat'd in EtOH)(ml)	EtOH/H2O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
1.620	6.50	6.50 / 6.50	3.00	16	I-c179-I	0.737

Reaction4

I-c179-I (g)	ZCl (ml)	Na_2CO_3 (g)	Dioxane/ H_2O (ml)	Reaction time (hr)	Product	Amount (g)
0.737	0.45	0.450	9.00 / 9.00	1	I-d179-I	1.090

Reaction5

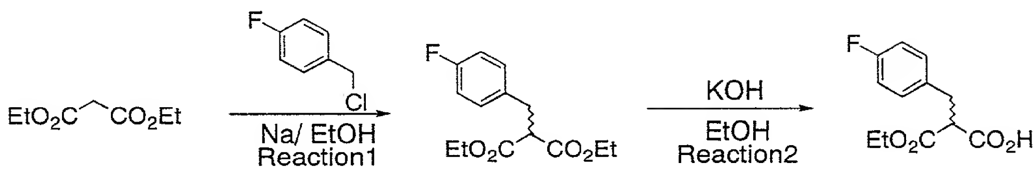
I-d177-I (g)	NaOH (g)	EtOH/H_2O (ml)	Reaction time (hr)	Amount (g)
1.090	0.186	9.00 / 9.00	1.5	1.010

(Reference Example 28)

Synthesis of Intermediate P9

The synthesis scheme is shown below.

Synthesis scheme of Intermediate P9



Diethyl malonate | I-a180-I | P9

The synthesis method of Intermediates P9 is explained below.

Reaction step 1)

To a solution of Na-metal in ethanol, diethyl malonate and 4-(chloromethyl)-1-fluorobenzene were added dropwise and then stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give Compound I-a180-I in a crude form.

Reaction step 2)

To a solution of Compound I-a180-I in ethanol, KOH was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water and washed with Et_2O. The aqueous layer was

adjusted to a pH of 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Intermediate P9.

Result is shown in Table E-49.

Table E-49

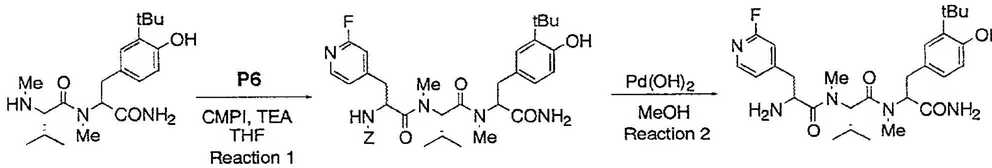
Intermediate P9

2-(Ethoxycarbonyl)-3-(4-fluorophenyl)propanoic acid

Reaction1					
Diethyl malonate (g)	4-(chloromethyl)-1-fluorobenzene (ml)	Na-metal (g)	EtOH (ml)	Product	Amount (g)
15.000	10.90	2.180	120.00	I-a180-I	25.000
Reaction2					
I-a180-I (g)	KOH (g)	EtOH (ml)	Amount (g)		
2.160	5.170	160.00	1.400		

The synthesis scheme of Examples 177A to 179B is shown in Scheme 15.

Scheme 15: Synthesis scheme of Examples 177A to 179B



N-Me-Val-N-Me-Tyr	I-a177A (less polar)	Example 177A(less polar)
(3-tBu)-NH_2	I-a177B (more polar)	Example 177B(more polar)

Referring to Examples 177A and 177B, the synthesis process of Scheme 15 is explained below:

Reaction step 1)

To a solution of Comound P6, N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a177A (less polar) and Compound I-a177B (more polar).

Reaction step 2)

To solutions of Compound I-a177A (less polar) and Compound I-a177B (more polar) in methanol, $Pd(OH)_2$ was added and stirred in a hydrogen atmosphere at room

temperature. After filtering off the $Pd(OH)_2$, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Example 178 (178A and 178B) and Example 179 (179A and 179B) were conducted similar to the above, except that P7 and P8 were employed, respectively, instead of P6.

Examples conducted according to Scheme 15 are shown in Tables D-177A to D-179B.

Table D-177A

Example 177A:Less polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl ethyl}-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoyla mino]-3-methyl-N-methylbutanamide

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Compound P6(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.776	0.886	0.711	0.45	30.00	16	nHx:EA=1:1	I-a177A	0.275
							I-a177B	0.288

Reaction2

Compound I-a177A(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.275	0.042	20.00	3	MC:MeOH =20:1	0.160	17.50

ESI-MS(M^++1):530

1H-NMR($CDCl_3$): (two rotamers) δ 0.32, 0.42 and 0.60, 0.88(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.20(1H, m), 2.52 and 2.91, 2.95(6H, s), 2.60-3.28(4H, m), 2.95(3H, s), 3.75(1/2H, dd, J=8.8, 6.1Hz), 3.95(1/2H, t, J=8.8Hz), 4.65 and 5.00(1H, d, J=8.8Hz), 4.96 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.60 and 6.05(1H, brs), 6.60 and 6.15(1H, d, J=8.8Hz), 6.70 and 7.04(2H, m), 6.92 and 7.12(2H, m), 8.12(1H, m)

Table D-177B

Example 177B: more polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a177B(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.288	0.043	20.00	3	MC:MeOH =20:1	0.160	15.48
ESI-MS(M^++1):530						
1H-NMR($CDCl_3$): (two rotamers) δ 0.46, 0.72 and 0.78, 0.91(6H, d, J=7.1-7.9Hz), 1.32 and 1.38(9H, s), 2.15-2.40(1H, m), 2.50, 2.83, and 3.0, 3.08(6H, s), 2.40-3.40(5H, m), 3.70 and 3.90(1H, dd, J=8.8, 3.5-4.4Hz), 4.81 and 5.05(1H, d, J=9.7Hz), 4.99 and 5.52(2H, m), 6.05 and 6.49(1H, brs), 6.48 and 6.64(1H, d, J=7.9Hz), 6.74 and 6.76, 6.82(2H, brs), 6.90-7.18(2H, m), 8.12(1H, d, J=6.2Hz)						

Table D-178A

Example 178A:less polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Compound P7(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.140	0.917	0.58	20.00	3	nHx:EA=1:1	I-a178A	0.380
							I-a178B	0.100

Reaction2

Compound I-a178A(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.380	0.057	10.00	3	MC:MeOH =20:1	0.210	17.76

ESI-MS(M^++1):530

1H-NMR($CDCl_3$): (two rotamers) δ 0.32, 0.42 and 0.60, 0.89(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.30(1H, m), 2.50, 2.90 and 2.94, 2.95(6H, s), 2.58-3.29(4H, m), 3.70(1/2H, dd, J=8.8, 6.1Hz), 3.90(1/2H, t, J=8.8Hz), 4.67 and 5.04(1H, d, J=8.8Hz), 4.95 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.70(1H, brs), 6.05 and 6.55(1H, brs), 6.58 and 6.65(1H, d, J=8.8Hz), 6.75-6.99(2H, m), 7.10 and 7.18(1H, brs), 7.58-7.75(1H, m), 8.12(1H, m)

Table D-178B

Example 178B: more polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a178B(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.100	0.015	5.00	3	MC:MeOH =20:1	0.040	15.65
ESI-MS(M^++1):530						
1H-NMR($CDCl_3$): (two rotamers) δ 0.50, 0.75 and 0.77, 0.95(6H, d, J=7.1-7.9Hz), 1.32 and 1.39(9H, s), 2.00-2.30(1H, m), 2.47, 2.83 and 3.0, 3.05(6H, s), 2.18-3.42(4H, m), 3.61 and 3.82(1H, dd, J=8.8, 3.5-4.0Hz), 4.85 and 5.07(1H, d, J=9.7Hz), 5.57 and 5.70, 5.79, 6.11(2H, m and brs), 6.55 and 6.65(1H, d, J=7.9-8.8Hz), 6.73, 6.88 and 6.97(2H, m), 7.13(1H, brs), 7.60-7.75(1H, m), 7.97 and 8.05(1H, brs)						

Table D-179A

Example 179A:less polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino}-3-methyl-N-methylbutanamide

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Compound P8(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.626	0.435	0.3	30.00	3	nHx:EA=1:1	I-a179A	0.330
							I-a179B	0.332

Reaction2

Compound I-a179A(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.330	0.049	10.00	3	MC:MeOH =20:1	0.136	19.89

ESI-MS(M^++1):579

1H-NMR($CDCl_3$): (two rotamers) δ 0.49, 0.74 and 0.79, 0.93(6H, d, J=6.3-6.8Hz), 1.34 and 1.39(9H, s), 2.25-2.48(1H, m), 2.53, 2.79 and 3.01, 3.05(6H, s), 2.58-3.40(4H, m), 3.74 and 3.90(1H, m), 4.87 and 5.07(1H, d, J=10.5-10.9Hz), 5.38-5.10(2H, m), 6.20(2/3H, brs), 6.40 and 6.65(1H, d, J=7.9Hz), 6.58(1/3H, brs), 6.73 and 6.97(1H, d, J=7.9-8.4Hz), 7.12(1H, m), 7.27-7.30(2H, m), 7.55-7.60(2H, m)

Table D-179B

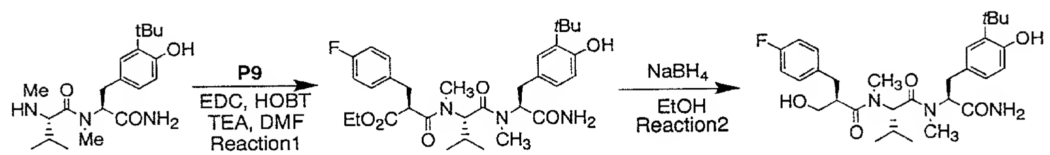
Example 179B: more polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino}-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a179B(g)	$Pd(OH)_2$ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.332	0.049	10.00	3	MC:MeOH =20:1	0.123	22.09
ESI-MS(M^++1):579						
1H-NMR($CDCl_3$): (two rotamers) δ 0.33, 0.36 and 0.55, 0.87(6H, d, J=6.4-6.9Hz), 1.37 and 1.41(9H, s), 2.00-2.20(1H, m), 2.56, 2.92 and 2.98(6H, s), 2.60-3.21(4H, m), 3.77 and 3.96(1H, m), 4.67 and 5.02(1H, d, J=10.6-10.9Hz), 4.96 and 5.45(1H, dd, J=9.0-11.3, 3.4-6.0Hz), 5.67 and 6.04(1H, brs), 6.57 and 6.63(1H, d, J=7.9Hz), 6.74 and 6.94(1H, dd, J=8.0-9.8, 1.8-2.1Hz), 7.08 and 7.16(1H, d, J=1.9Hz), 7.27-7.37(2H, m), 7.52-7.60(2H, m)						

Scheme 16 shows synthesis process of Examples 180A and B.

Scheme 16: synthesis process of Examples 180A and B



N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 | I-a180A (less polar), I-a180B (more polar) | Example 180A (less polar), Example 180B (more polar)

The synthesis process of Scheme 16 is explained below.

Reaction step 1)

To a solution of Compound P9, N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, EDCL and HOBT in DMF, TEA was added under

cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel) to give Compound I-a180A (less polar) and Compound I-a180B (more polar).

Reaction step 2)

To the solutions of Compound I-a180A (less polar) and Compound I-a180B (more polar) in ethanol, $NaBH_4$ was added under cooling and stirred at room temperature. The reaction mixtures were mixed with a 1N HCl solution, extracted with Et_2O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds (less polar compound and more polar compound).

Tables D-180A and B show Examples conducted according to Scheme 16.

Table D-180A

Example 180A: Less polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpropanoylamino}-3-methyl-N-methylbutanamide

Reaction1									
N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Compound P9(g)	EDCI (g)	HOBT (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	1.29	1.030	0.824	1.08	30.00	2.5	nHx:EA=1:1	I-a180A	0.700
								I-a180B	0.820

Reaction2						
Compound I-a180A(g)	$NaBH_4$ (g)	EtOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.700	0.490	30.00	3	MC:MeOH=20:1	0.17	21.83

ESI-MS(M^++1):544

1H-NMR($CDCl_3$): (two rotamers) δ 0.48, 0.74 and 0.76, 0.92(6H, d, J=6.0-7.2Hz), 1.35 and 1.39(9H, s), 2.05-2.50(1H, m), 2.50, 2.80 and 2.98, 3.01(6H, s), 2.40-3.36(5H, m), 3.50-3.70(2H, m), 3.50-3.70(2H, m), 4.90 and 5.08(1H, d, J=10.6Hz), 5.45(1H, m), 5.50 and 6.05(1H, brs), 5.70 and 6.20(1H, brs), 6.44 and 6.64(1H, d, J=8.8-8.3Hz), 6.73-7.15(7H, m)

Table D-180B

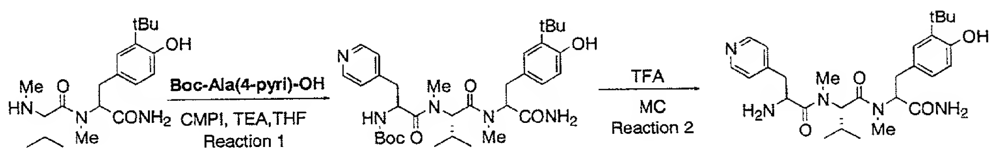
Example 180B: more polar

(2S)-N-{(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl}-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpropanoylamino}-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a180B(g)	$NaBH_4$ (g)	EtOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC / min
0.820	0.492	30.00	3	MC:MeOH =20:1	0.060	23.95
ESI-MS(M^++1):544						
1H-NMR($CDCl_3$): (two rotamers) δ 0.17-0.20 and 0.44, 0.84(6H, m and d, J=6.5-6.7Hz), 1.36 and 1.40(9H, s), 2.00-2.20(1H, m), 2.41 and 2.90, 2.92(6H, s), 2.67-4.00(13H, m),4.73 and 5.00(1H, d, J=10.5Hz), 5.20 and 5.35(1H, m), 5.83 and 6.18(1H, brs), 6.38 and 6.51(1H, brs), 6.62 and 6.65(1H, d, J=7.9Hz), 6.75-7.20(8H, m)						

The synthesis scheme of Examples 181 and 182 is shown in Scheme 17.

Scheme 17: Synthesis scheme of Examples 181 and 182



N-Me-Val-N-Me- Tyr (3-tBu)-NH_2 I-a181   Example 181

Referring to Example 181, the synthesis process of Scheme 17 is explained below:

Reaction step 1)

To a solution of Comound Boc-Ala(β-4-pyridyl)-OH, N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a181.

Reaction step 2)

To a solution of Compound I-a181 in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under

reduced pressure, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Compound of Example 182 was obtained according to a similar process to Example 181 using Boc-Ala(β-4-pyridyl)-OH.

Examples conducted according to Scheme 17 are shown in Tables D-181 and D-182.

Table D-181

Example 181

Ala(β-4-pyridyl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Boc-Ala(beta-4-pyridyl)-OH (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.680	0.500	0.960	0.52	15.00	24	MC:MeOH =30:1	I-a181	0.800

Reaction2

Compound I-a181(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.800	4.00	20.00	3	MC:MeOH =20:1	0.450	13.30

ESI-MS(M^++1):512

1H-NMR($CDCl_3$): (two rotamers) δ 0.40, 0.72 and 0.82, 0.96(6H, d, J=6.3-6.7Hz), 1.37 and 1.42(9H, s), 2.05-2.30(1H, m), 2.51, 2.89 and 2.94, 2.96(6H, s), 2.59-3.30(4H, m), 4.65-5.05(1H, m), 5.30(1H, s), 5.45-5.05(1H, m), 6.30-6.45(1H, m), 6.60-7.05(2H, m), 7.10-7.20(2H, m), 8.20-8.25(2H, m)

Table D-182

Example 182

Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Boc-Phe(4-CN)-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.500	0.660	0.48	15.00	24	MC:MeOH =30:1	I-a182	0.900

Reaction2

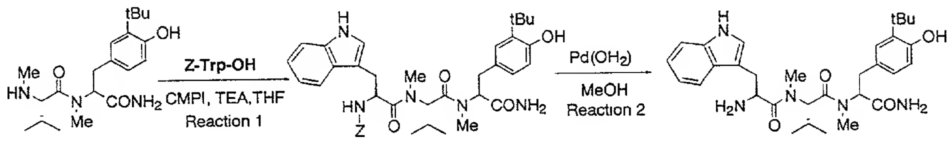
Compound I-a182(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.900	4.00	20.00	4	MC:MeOH =20:1	0.520	16.82

ESI-MS(M^++1):536

1H-NMR($CDCl_3$): (two rotamers) δ 0.48, 0.76 and 0.85, 0.94(6H, d, J=6.3-6.8Hz), 1.37 and 1.43(9H, s), 2.20-2.70(1H, m), 2.55, 2.85 and 2.95, 3.05(6H, s), 3.15-3.40(2H, m), 3.65-3.85(2H, m), 4.75-5.20(2H, m), 5.40-5.50(1H, m), 6.40-6.65(1H, m), 6.75-6.85(1H, m), 6.95-7.15(1H, m), 7.25-7.35(2H, m), 7.58-7.63(2H, m)

The synthesis scheme of Example 183 is shown in Scheme 18.

Scheme 18: Synthesis scheme of Example 183



N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 | I-a183 | Example 183

The synthesis process of Scheme 18 is explained below:

Reaction step 1)

To a solution of Z-Trp-OH,N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a183.

Reaction step 2)

To a solution of Compound I-a183 in methanol, $Pd(OH)_2$ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the $Pd(OH)_2$, the filtrate was concentrated under reduced pressure; the thus

obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Example conducted according to Scheme 18 is shown in Table D-183.

Table D-183

Example 183

Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

Reaction1

N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (g)	Z-Trp-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.700	0.660	0.48	15.00	24	MC:MeOH =30:1	I-a183	0.700

Reaction2

Compound I-a183(g)	$Pd(OH)_2$	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.700	0.100	20.00	24	MC:MeOH =20:1	0.380	18.14

ESI-MS(M^++1):550

1H-NMR($CDCl_3$): (two rotamers) δ 0.39, 0.73 and 0.79, 0.93(6H, d, J=6.3-6.7Hz), 1.33 and 1.39(9H, s), 2.15-2.35(2H, m), 2.37, 2.75 and 2.95, 3.05(6H, s), 2.60-3.15(2H, m), 3.25-3.40(2H, m), 3.80-4.05(1H, m), 4.70-5.10(1H, m), 6.30-6.55(1H, m), 6.65-7.20(5H, m), 7.40-7.60(2H, m)

Test Example 1

Motilin receptor binding test

A motilin receptor binding test was conducted in the following manner [Vantrappen et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered rabbit, had the mucous membrane separated and homogenized in 50 mM Tris buffer to prepare a protein sample. The protein sample was incubated together with ^{125}I motilin 25 pM and thereafter the radioactivity bound to the protein was measured. Specific binding was defined as the difference between the radioactivity in the case of adding a great excess amount of motilin (10^{-7} M) and that in the case of no adding. The activity of the compound was expressed by IC_{50} (in nM), as the concentration sufficient to reduce the specific binding by 50%. Result is shown in Tables F-1 to F-3.

Test Example 2

Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit was investigated by the following method. A duodenum specimen (5 x 15 mm) extracted from a slaughtered rabbit was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was filled with a Krebs solution kept at 28°C. A mixed gas (95% O_2 and 5% CO_2) was continuously bubbled into the Krebs

solution and the contraction of the duodenum specimen was recorded isotonically (with a 1-g load) via an isotonic transducer (ME-3407, ME Commercial, Tokyo, Japan). The degree of contraction was expressed in relative values, with the contraction by acetylcholine at a dose of 10^{-4} M being taken as 100%. The activity of the compound was calculated as pA_2 value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The result is shown in Tables F-1 to F-3.

Table F-1

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
1	0.89	8.8
2	0.71	8.7
3	1.5	8.7
4	1.6	8.3
8	0.35	9.5
9	1.0	9.0
12	0.52	9.3
14	0.70	9.3
15	0.82	8.5
16	0.41	9.4
17	0.70	9.1
19	2.2	8.7
21	0.27	9.8
22	0.52	8.3
23	0.67	9.3
24	0.94	9.1

Table F-2

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
26	7.3	8.0
27	1.2	8.6
28	0.52	9.0
29	0.45	8.7
30	0.81	9.1
31	0.79	9.5
32	0.76	9.1
33	1.7	8.4
34	1.5	9.4
35	1.7	8.8
36	2.3	8.8
37	0.60	8.8
38	3.0	8.2
39	2.0	8.7
40	1.6	8.6
41	3.1	8.4
42	1.2	8.3
43	1.9	8.5
44	3.6	8.5
63	0.62	8.4
64	1.0	9.0
101	0.24	8.9
102	0.31	9.0
103	0.86	8.9

Table F-3

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
104	0.32	9.1
105	0.31	9.8
106	0.62	9.8
107	0.39	8.7
108	0.43	9.0
109	0.17	8.7
119	0.40	9.4
120	0.27	9.0
121	0.41	8.9
122	0.47	9.0
123	0.70	9.1
124	0.98	9.1
125	1.0	9.0
126	1.9	9.2
127	1.7	8.7
128	1.5	8.7
129	4.0	8.5
132	0.86	8.9

Table F-4

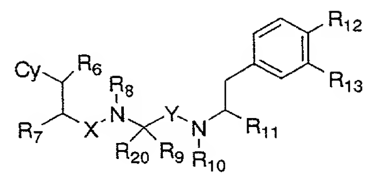
Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
133	1.1	8.2
134	1.5	8.3
135	0.70	8.5
136	6.8	7.6
140	4.0	8.2
142	0.62	8.6
144	2.0	8.5
148	4.1	8.4
151	0.36	8.2
155	2.5	8.1
157	6.1	8.1
163	2.4	7.8
165	2.8	8.2
166	1.8	9.8
182	2.3	8.5
183	0.57	9.5

INDUSTRIAL APPLICABILITY

The compounds of the present invention function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.

CLAIMS

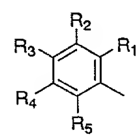
1. A compound of Formula (1):



(1)

wherein:

Cy is a group of Formula (2):



(2)

an optionally substituted heterocyclic ring, C_{3-7}cycloalkyl or phenyl;

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy, amino, trifluoromethyl or nitrile and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen, trifluoromethyl or nitrile;

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

R_7 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

R_8 is hydrogen, methyl or ethyl;

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, optionally substituted straight-chained or branched C_{2-6}alkenyl, optionally substituted straight-chained or branched C_{2-6}alkynyl, C_{3-7}cycloalkyl or

optionally substituted phenyl;

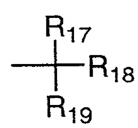
R_{20} is hydrogen or straight-chained or branched C_{1-3}alkyl or R_9 and R_{20} may together form C_{3-7}cycloalkyl;

R_{10} is hydrogen or straight-chained or branched C_{1-3}alkyl;

R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15}, carboxyl or an optionally substituted heterocyclic ring;

R_{12} is hydroxy or -OR_{16};

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl, straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (3):



(3)

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4}alkyl, C_{3-7}cycloalkyl, straight-chained or branched C_{1-4}alkyloxy, straight-chained or branched C_{1-4}alkylsulfonyl or a heterocyclic ring, or R_{14} and R_{15}, as -N(R_{14})R_{15}, form optionally substituted 3- to 7-membered cyclic amine;

R_{16} is straight-chained C_{1-4}alkyl;

R_{17} is hydrogen or methyl;

R_{18} and R_{19} together form cycloalkyl or C_{3-7}cycloalkenyl;

X is carbonyl or methylene;

Y is carbonyl or methylene;

provided that

when Cy is 3-indolyl,

(i) R_{11} is an optionally substituted heterocyclic ring; or

(ii) R_6 is hydrogen, R_7 is amino, R_8 is methyl, R_9 is isopropyl, R_{20} is hydrogen, R_{10} is methyl, R_{11} is carbamoyl, R_{12} is hydroxy, R_{13} is tert-butyl, X is carbonyl and Y is carbonyl, and

when Cy is cyclohexyl or phenyl, R_{11} is an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2); or a hydrate or pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy; or a hydrate or pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which R_3 is halogen or R_2 and R_3 are the same kind of halogen; or a hydrate or pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which R_3 is halogen and R_1, R_2, R_4 and R_5 are hydrogen, or

R_2 and R_3 are the same kind of halogen and R_1, R_4 and R_5 are hydrogen;

or a hydrate or pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is trifluoromethyl and the others are hydrogen, halogen or hydroxy;

or a hydrate or pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is nitrile and the others are hydrogen, halogen or hydroxy;

or a hydrate or pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which R_3 is trifluoromethyl;

or a hydrate or pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein Cy in Formula (1) is a group of Formula (2) in which R_3 is nitrile;

or a hydrate or pharmaceutically acceptable salt thereof.

10. The compound according to claim 1, wherein Cy in Formula (1) is an optionally substituted heterocyclic ring provided that when Cy is 3-indolyl,

(i) R_{11} is an optionally substituted heterocyclic ring; or

(ii) R_6 is hydrogen, R_7 is amino, R_8 is methyl, R_9 is

isopropyl, R_{20} is hydrogen, R_{10} is methyl, R_{11} is carbamoyl, R_{12} is hydroxy, R_{13} is tert-butyl, X is carbonyl and Y is carbonyl;

or a hydrate or pharmaceutically acceptable salt thereof.

11. The compound according to claim 1, wherein in Formula (1), Cy is C_{3-7}cycloalkyl provided that when Cy is cyclohexyl, R_{11} is an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

12. The compound according to claim 1, wherein in Formula (1), Cy is phenyl and R_{11} is an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-12, wherein R_6 in Formula (1) is hydrogen or methyl;

or a hydrate or pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1-13, wherein R_7 in Formula (1) is hydrogen or optionally substituted amino;

or a hydrate or pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1-14, wherein R_8 in Formula (1) is hydrogen or methyl;

or a hydrate or pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1-15, wherein R_9 in Formula (1) is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, cyclohexylmethyl or para-fluorobenzyl;

or a hydrate or pharmaceutically acceptable salt thereof.

17. The compound according to any one of claims 1-16, wherein R_{20} in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

18. The compound according to any one of claims 1-17, wherein R_{10} in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 1-18, wherein R_{11} in Formula (1) is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tertbutylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl, 6-methyl-4-pyrimidinon-2-yl, methylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl or 4-methylsulfonyl-1-piperazinecarbonyl;
or a hydrate or pharmaceutically acceptable salt thereof.

20. The compound according to any one of claims 1-19, wherein R_{12} in Formula (1) is hydroxy;
or a hydrate or pharmaceutically acceptable salt thereof.

21. The compound according to any one of claims 1-20, wherein R_{13} in Formula (1) is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

22. The compound according to claim 1, wherein in Formula (1)

Cy is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy;

R_6 is hydrogen or methyl;

R_7 is hydrogen or optionally substituted amino;

R_8 is hydrogen or methyl;

R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or cyclohexylmethyl;

R_{20} is hydrogen;

R_{10} is hydrogen or methyl;

R_{11} is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl;

R_{12} is hydroxy;

R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or

1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

23. The compound according to claim 1 which is selected from the group of compounds consisting of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea, N-(2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalanyloyl)methylamino]-3-methylbutanamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tertbutyl-4-

hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide, Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val- N-Et-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2SO_2CH_3$, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, N-Et-

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHEt, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHEt, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)- NHEt, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHEt, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-$NHCH_2OH$, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHcPr, and Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHnPr Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHiPr;

or a hydrate or pharmaceutically acceptable salt thereof.

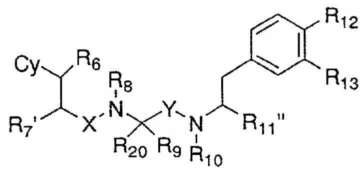
24. A medicine containing the compound according to any one of claims 1-23 as an active ingredient

25. A motilin receptor antagonist containing the compound according to any one of claims 1-23.

26. A gastrointestinal motility suppressor agent containing the compound according to any one of claims 1-23 as an active ingredient

27. A therapeutic of hypermotilinemia containing the compound according to any one of claims 1-23 as an active ingredient.

28. A compound of Formula (4):



(4)

wherein

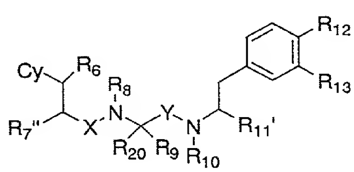
Cy, R_6, R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13}, X and Y are as defined in claim 1;

R_7' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one protected substituent, amino optionally having at least one protected substituent or protected hydroxy; and

R_{11}'' is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15}, wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having a protected amino or an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

29. A compound of Formula (5):



(5)

wherein:

Cy, R_6, R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13}, X and Y are as defined in claim 1;

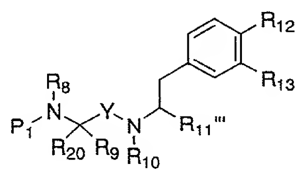
R_7'' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally

protected hydroxy; and

R_{11}' is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one protected substituent, $-CO-N(R_{14})R_{15}$ wherein R_{14} and R_{15} are as defined in claim 1, carboxyl or an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

30. A compound of Formula (6):



(6)

wherein:

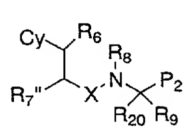
R_8, R_9, R_{20}, R_{10}, R_{12}, R_{13} and Y are as defined in claim 1;

P_1 is hydrogen or a protecting group of amine; and

R_{11}''' is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, $-CO-N(R_{14})R_{15}$ wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having protected amino or an optionally substituted heterocyclic ring;

or a hydrate or pharmaceutically acceptable salt thereof.

31. A compound of Formula (7):



(7)

wherein:

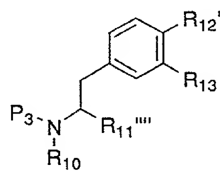
Cy, R_6, R_8, R_9, R_{20} and X are as defined in claim 1;

R_7" is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy; and

P_2 is optionally protected carboxyl, formyl or methyl which has a leaving group;

or a hydrate or pharmaceutically acceptable salt thereof.

32. A compound of Formula (8):



(8)

wherein:

R_{10} and R_{13} are as defined in claim 1;

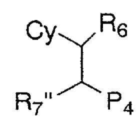
P_3 is hydrogen or a protecting group of amine;

R_{11}'''' is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15} wherein R_{14} and R_{15} are as defined in claim 1, carboxyl, straight-chained or branched C_{1-3}alkyl having protected amino or an optionally substituted heterocyclic ring; and

R_{12}' is hydroxy or -OR_{16} wherein R_{16} is as defined in claim 1;

or a hydrate or pharmaceutically acceptable salt thereof.

33. A compound of Formula (9):



(9)

wherein:

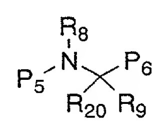
Cy and R_6 are as defined in claim 1;

R_7" is hydrogen, straight-chained or branched C_{1-3}alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy; and

P_4 is optionally protected carboxyl, formyl or methyl which has a leaving group;

or a hydrate or pharmaceutically acceptable salt thereof.

34. A compound of Formula (10):



(10)

wherein:

R_8, R_9 and R_{20} are as defined in claim 1;

P_5 is hydrogen or a protecting group of amine; and

P_6 is optionally protected carboxyl, formyl or methyl which has a leaving group;

or a hydrate or pharmaceutically acceptable salt thereof.

 [X] Original [ ] Supplemental Atty. Docket:

#3

Combined Declaration for Patent Application and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and that I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

SUBSTITUTED PHENETHYLAMINE DERIVATIVES

the specification of which (check one)

[ ] is attached hereto;

[ ] was filed in the United States under 35 U.S.C. §111 on ________________, as U.S. Appln. No. __________*; or

[X] was/will be filed in the U.S. under 35 U.S.C. §371 by entry into the U.S. national stage of an international (PCT) application, PCT/JP00/00444 filed Jan. 28, 2000, entry requested on ________________*; national stage application received U.S. Appln. No. __________*; §371/§102(e) date ________________* (* if known)

and was amended on ____ (if applicable).

(include dates of amendments under PCT Art. 19 and 34 if PCT)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; and I acknowledge the duty to disclose to the Patent and Trademark Office (PTO) all information known by me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119 and 365 of any prior foreign application(s) for patent or inventor's certificate, or prior PCT application(s) designating a country other than the U.S., listed below with the "Yes" box checked and have also identified below any such application having a filing date before that of the application on which priority is claimed:

(Number)	(Country)	(Day Month Year Filed)	YES	NO
20523/1999	Japan	28/1/1999	[X]	[ ]
283163/1999	Japan	4/10/1999	[X]	[ ]

I hereby claim the benefit under 35 U.S.C. §120 of any prior U.S. non-provisional application(s) or prior PCT application(s) designating the U.S. listed below, or under §119(e) of any prior U.S. provisional applications listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in such U.S. or PCT application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the PTO all information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application and the national filing date of this application:

(Application No.)	(Day Month Year Filed)	(Status: patented, pending, abandoned)

As a named inventor, I hereby appoint the following registered practioners to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

All of the practioners associated with Customer Number 001444

Direct all correspondence to the address associated with **Customer Number 001444**; i.e.,

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, D.C. 20001-5303
(202) 628-5197

The undersigned hereby authorizes the U.S. Attorneys or Agents appointed herein to accept and follow instructions from YUASA AND HARA as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. Attorneys or Agents and the undersigned. In the event of a change of the persons from whom instructions may be taken, the U.S. Attorneys or Agents appointed herein will be so notified by the undersigned.

Atty. Docket:

Title: SUBSTITUTED PHENETHYLAMINE DERIVATIVES

U.S. Application filed __________, Serial No. __________

PCT Application filed January 28, 2000, Serial No. PCT/JP00/00444

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

FULL NAME OF FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
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2-00

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3-00

FULL NAME OF THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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4-00

FULL NAME OF FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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5-00

FULL NAME OF FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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POST OFFICE ADDRESS: 103-1004 Keukdong Apt., 50 Maetan 2-dong, Paltal-gu, Suwon-si, 442-372 Kyunggi-do Republic of Korea		

6-00

FULL NAME OF SIXTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Chan Hee PARK	Chan Hee Park	Aug. 20,2001
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FULL NAME OF SEVENTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENT:		CITIZENSHIP:
POST OFFICE ADDRESS:		

ALL INVENTORS MUST REVIEW APPLICATION AND DECLARATION BEFORE SIGNING. ALL ALTERATIONS MUST BE INITIALED AND DATED BY ALL INVENTORS PRIOR TO EXECUTION NO ALTERATIONS CAN BE MADE AFTER THE DECLARATION IS SIGNED ALL PAGES OF DECLARATION MUST BE SEEN BY ALL INVENTORS.